Key Documents of the Biomedical Aspects of Deep-Sea Diving

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OTOLOGY IN DIVING (THE EAR IN DIVING)

Articles selected by Joseph C. Farmer, Jr., M.D.
Duke University Medical Center
Durham, North Carolina

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OTOLOGY IN DIVING
(The Ear in Diving)

JOSEPH C. FARMER, JR.

Numerous articles concerning otologic problems in diving have appeared since A. H. Smith in his 1873 description of "caisson disease" listed severe deafness and vestibular problems among other systemic injuries in compressed air workers. During the remainder of the 19th century, other investigators made specific contributions in this field. The most notable was Alt (1897), working with Heller, Mager and von Schrotter (Alt et al. 1897), who studied caisson workers at Nussdorf and described injuries to the middle and inner ear during compression and decompression. He further studied inner ear pathology in animals after rapid decompression and was the first to suggest that inner ear injuries in divers could occur during compression in association with inadequate middle ear pressure equilibration and during decompression, where the injuries were felt to be secondary to interference with the inner ear blood supply by nitrogen bubbles developing in the labyrinthine vasculature.

In 1929, Vail also noted that middle and inner ear injuries occurred in compressed air workers during compression and decompression. He described animal studies with histologic observations and suggested that inner ear damage during compression was related to inadequate middle ear pressure equalization, with resulting stasis and hemorrhage in the inner ear. He also hypothesized that such injury during decompression was related to nitrogen bubbles causing emboli or necrosis in the inner ear.

By 1940, safety procedures for air diving had improved and the frequency of inner ear injuries in association with diving apparently decreased. Much of the literature was devoted to prevention and treatment of barotitis media, a frequent problem. This was felt to be reversible and usually not resulting in serious disability. Inner ear injuries related to diving were felt to be rare. Notable publications regarding barotitis media include articles by Behnke (1944), and Shilling and Everley (1942). Taylor (1959) further described middle ear barotrauma as well as other diving-related ENT problems in a key review article; not reproduced because of page limitations.

Noteworthy publications concerning the function of the nontraumatized auditory and vestibular systems during diving appeared during the 60's and 70's. These articles include the work of Fluur and Adolfson (1966), who were among the first to study the hearing of humans during hyperbaric air exposures using calibrated transducers; Thomas et al. (1974) (summary included in review by Farmer and Thomas, 1975), who published extensive measurements of hearing thresholds of divers during simulated helium-oxygen exposures to 1000 ft; Braithwaite et al. (1974), who performed measurements of balance and vestibular functions in humans exposed to depths of 487.5 m; and Brandt and Hollien (1969), who published work concerning underwater hearing thresholds and mechanisms.

In recent years, commercial, military, and sport diving to deeper depths has increased, and reports of otologic disturbances, particularly inner ear disturbances, during all types and phases of diving have appeared more frequently. In 1974, Kennedy published an article on "General History of Vestibular Disorders in Diving" in which he reviewed the literature extensively and summarized vertigo and disequilibrium symptoms related to diving, including case histories, incidences, and other factors. Edmonds et al., in 1973, in a book entitled *Otological Aspects of Diving*, undertook a detailed review of the various causes due to unequal vestibular stimulations, including caloric stimulations, barotrauma causes, decompression sickness, and causes due to unequal vestibular responses to equal stimuli. These works are important documents which should be considered in any review of this subject, although page limitations prevent duplication here.

Lundgren (1965) contributed significantly to understanding transient vestibular dysfunction in diving with his description of inadequate middle ear pressure equilibration and subsequent vertigo during ascent. He termed this phenomenon alternobaric vertigo. Ingelstedt et al. (1974) later demonstrated and defined the problem experimentally in simulated chamber exposures. A summary of these efforts appears in a reproduced review article (Farmer, 1977).

In 1975, Farmer and Thomas published a chapter in *The Physiology and Medicine of Diving and Compressed Air Work*, edited by Bennett and Elliott, which completely reviewed the entire subject, including reviews of the basic anatomy and physiology of the hearing and balance organs, and discussions of how these organs may be affected by physical stresses encountered in diving. A modification of Edmonds' classification was offered, which separated diving otologic problems into ones noted as transient and ones resulting from permanent inner ear injuries. A later publication by Farmer (1977) reviewed inner ear diving injuries and indicated that the causes and treatment of these problems differed, depending upon the phase of diving in which the injuries occurred. Persistent inner ear injuries were classified into: (1) injuries occurring during decompression (inner ear narotrauma); (2) injuries occurring after changes in inspired inert gases at stable deep depths; (3) inner ear injuries related to decompression sickness; and (4) injuries secondary to excessive noise exposure in diving. These two articles are reproduced since they review the work of others who have made important contributions to this field.

Significant articles concerning inner ear injuries during the compression phase of shallow diving have been published by Freeman and Edmonds (1972), and Edmonds et al. (1974). These investigators defined the major pathology of such injuries to be labyrinthine window ruptures associated with inadeuate middle ear pressure equilibration during compression. They were the first modern writers after Alt (1897) and Vail (1929), published years earlier, to indicate to the diving community that middle ear barotrauma during compression can result in significant inner ear injury leading to vertigo, with nausea and vomiting at depth and/or permanent disability. They further postulated that such injuries may not be as uncommon, particularly among sport divers, as previously thought. Appropriate post-injury management techniques were also presented.

Lambertsen and Idicula (1975) contributed significantly to this subject, describing inner ear vestibular dysfunction and injury occurring in humans while at stable deep depth, soon after onset of breathing different inert gases. This is the only time inner ear injuries occurring under these conditions have been well described, and represents an example of what is now recognized as the counterdiffusion phenomenon.

Since the early writings by Alt and Vail, several important publications concerning specific inner ear injuries occurring during decompression have appeared during the last 10 years. Stucker and Echols (1971) suggested that inner ear injuries during diving could occur from nitrogen bubble emboli forming in the internal auditory artery system. Rubenstein and Summitt (1971) described 10 cases of isolated vestibular and/or cochlear injuries occurring during or shortly after decompression. Buhlmann and Gehring (1976) described additional incidences of otologic injuries in humans related to decompression from deep helium-oxygen diving. McCormick et al. (1973) showed that guinea pigs subjected to rapid decompression developed intralabyrinthine bubble formations and hemorrhages plus decreases in cochlear electrical function along with other manifestations of decompression sickness. Landolt et al. (1977) well described vestibular dysfunction and inner ear pathology in monkeys after rapid decompression. Farmer et al. (1976), enlarging on the 10 cases of Rubenstein and Summitt, in 1978 published 23 cases of isolated vestibular and/or cochlear injuries occurring in humans during or shortly after decompression. A significant correlation between prompt recompression treatment and recovery was noted. Twelve of 19 helium exposures involved dives in which the otologic symptoms began with, or shortly after, a switch to air atmosphere during latter stages of decompression. Specific recommendations for management were reviewed.

OTOLOGY IN DIVING

J. C. FARMER, JR.

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PHYSIOLOGIC EFFECT OF PRESSURE CHANGES WITH REFERENCE TO OTOLARYNGOLOGY

A. R. BEHNKE, COMDR. (M.C.), U.S.N.
BETHESDA, MD.
BY INVITATION

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A. R. BEHNKE, Comdr. (M.C.), U.S.N.

BETHESDA, MD.

BY INVITATION

THE REMARKABLE phenomenon of adaptation to environmental stress is exemplified by man's tolerance to rapid and extreme alterations in barometric pressure. If pressure alone is considered apart from the effect of gases in the vicera, in the aural and sinal spaces and in solution in tissues, then variations in pressure in the range of 0.11 atmospheres (50,000 altitude) to 16.1 atmospheres (500 feet diving depth) are without physiologic effect.

Compression.—When the body is subjected to increased pressure, every air space, from the smallest and most inaccessible ethmoid cell to the air cells in the mastoid process, receives air provided that the passages to these spaces are unobstructed. The ingress of air to the aural spaces must be consciously brought about by the various maneuvers of swallowing, yawning, and Valsalva effort which relaxes tension on the normally closed "flutter valve" of the eustachian tube.

The rate of accommodation to increasing pressure in experienced individuals may be, in diving operations, as rapid as 45 pounds per square inch (2280 mm. Hg.) per minute which is equivalent to a diving descent at the rate of 100 feet per minute. In routine training operations, where factors other than the ability to equalize intra-tympanic pressure are present, the average time of descent to a depth of 225 feet by student divers making 400 dives was 5.2 minutes with a range of 2 to 14 minutes (table 1). In similar dives with helium-oxygen mixtures, the average time of descent to 225 feet in 400 dives was 4.6 minutes with a range of 2 to 15 minutes. For deep sea dives by experienced men (*USS Squalus* operations), the average time was about 3.5 minutes for depths of 225 to 240 feet. These average values ranging from 1.5 to 3.7 minutes per 100 feet do not represent maximal rates but rather rates that are well tolerated by healthy men and rates that do not produce trauma of sinal and aural membranes.

With respect to high altitude, simulated descents from 40,000 feet to sea level have been made in the low pressure chamber in 37 seconds without injury (table 1). In routine experimental simulated descents, the average rate of descent was 5000 feet per minute. This stands in contrast to a rate of 300 feet

U. S. Naval Research Institute, National Naval Medical Center, Bethesda, Maryland.

The opinions stated herein are those of the author and do not represent the official views of the Navy Department.

per minute as stipulated for commercial aviation to minimize the occurrence of aero-otitis media.[1]

It would appear from the data presented that less time is required for compression from 0.25 to 1 atmosphere than from 1 to 4 atmospheres. The number of deglutitions required by divers to equalize pressure on the two sides of the tympanic membrane in descent from 34,000 feet (0.25 atmosphere) to ground level and from the surface to a diving depth of 100 feet (4 atmospheres) are in the ratio of 7 to 13. If pressure is uniformly increased from 0.25 to 1 atmosphere during a period of 6 minutes and then, following a single 15 minute interval at ground level, increased to 4 atmospheres, it is observed that the pressure differences on the two sides of the tympanic membrane increase despite the fact that partial but not complete equilibration of pressure in the tympanum is apparently produced by each act of swallowing (fig. 1).

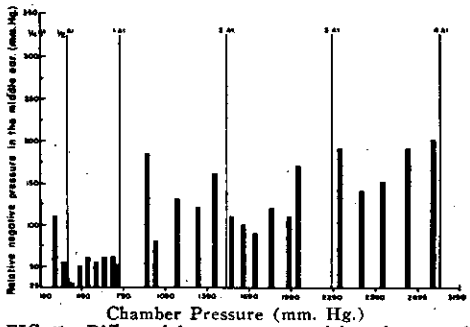

FIG. 1—Differential pressures requiring the act of swallowing for tympanic equilibration in continuous simulated descent from 33,500 feet (0.25 atmosphere) to ground level (1.0 atmosphere) in 6 minutes, and from 1 to 4 atmospheres (99 feet depths) in 6 minutes.

Even greater pressure differences on the two sides of the tympanic membrane are tolerated for short periods if stops are prolonged at each equilibration level to ensure complete pressure equalization using the Valsalva maneuver in addition to swallowing. A pressure difference, for example, of 115 mm. Hg. might require deglutition at 0.5 atmosphere (18,000 feet) for subjective comfort but at 4 atmospheres (100 feet diving depth) the corresponding difference might reach 350 mm. Hg. before subjective discomfort demanded equalization of pressure (fig. 2).

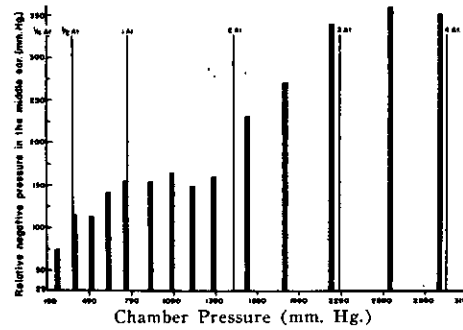

FIG. 2—Differential pressures requiring tympanic equilibration during descent from 33,500 feet to ground level and during compression from 1 to 4 atmospheres. At each level, stops were made to ensure complete pressure equilibrium by performance of the Valsalva maneuver and swallowing.

This is owing to the fact that, over a wide range of pressure, the subjective tolerance of the tympanum is seen to be related to a constant volume change rather than to a constant pressure difference. An increase of pressure, for example, from 1 to 2 atmospheres, tends to have an effect in producing subjective discomfort equivalent to an increase in pressure from 2 to 4 atmospheres since the volume change of intra-aural air is the same under both conditions. The problem of whether or not a constant pressure difference or a volume ratio governs the rate of compression is complicated by the fact that increases in density occur as the pressure is raised. To evaluate the factor of density, a helium-oxygen mixture was breathed in place of air as the pressure was raised from 1 to 4 atmospheres. The results showed that the rate of voluntary opening of the auditory tubes was not influenced by the density of the gas breathed (table 2). Subjects reported, however, that equalization of pressure was easier when they breathed the helium-oxygen mixture.

Decompression. — In contrast with compression, the release of air pressure from patent sinal and aural cavities can take place almost instantaneously without giving rise to symptoms.

Explosive decompressions simulating altitude increments of 20,000 feet and which tend to create excess pressure of 3.5 pounds per square inch (181 mm. Hg.) may be effected in a fraction of a second. Diving ascents likewise can be made from depths of 100 feet in less than 30 seconds.

Symptoms produced by differences in pressure. — Although air pressure has been increased to values as high as 225 pounds per square inch in sinal and aural spaces without demonstrable effect, small differences in pressure on the two sides of the tympanic membrane incident to tubal blockage of the order of 1 to 2 pounds per square inch (50 to 100 mm. Hg.) produce striking objective changes in the mucosa of the tympanum. The decreased or relative negative pressure in the tympanum compared with that present in the lining membrane exerts a "cupping action" to produce the familiar entity termed by Armstrong "aero-otitis media." This type of negative pressure injury (barotrauma) has been known since the beginning of diving and was studied in detail by Heller, Mager, and von Schrötter[10] who noted the hyperemia ex vacuo, congestion of the membranous lining of the middle ear and tympanic membrane, hemorrhage, and occasionally, perforation of the membrane. The pathologic picture, depending upon the pressure difference, shows, progressively, retraction of the tympanic membrane, gross dilation of blood vessels in Shrapnell's membrane and the malleolar area, and their subsequent rupture to produce exudation of serous fluid and blood into the middle ear, with final rupture of the tympanic membrane. The condition, except for retraction of the tympanic membrane, may grossly resemble an acute, infectious otitis media.

The "cupping action" affects not only the tympanic membrane but the whole membranous lining of the middle ear and mastoid cells. Similar changes take place in membranes lining obstructed sinuses.

The important observation is that a difference in pressure between the intraaural or intrasinal space and the lining membrane which is under the pressure of ambient air, elicits pain. With reference to the ear, pain is felt deep within the ear and over the parotid and mastoid areas which may also be tender to palpation. If the tympanic membrane of the occluded ear is inspected as the ambient pressure is increased, it may be noted that retraction of the tympanic membrane and engorgement of blood vessels precede pain. With reference to the sinuses pain is superficial and is distinguished by a sensation of multiple lancinating stimuli and by its sharp limitation to the affected area. Thus, a differential diagnosis between maxillary, ethmoidal, and frontal sinus closure may be made. The sphenoidal sinuses alone appear to be free from obstructive involvement. Palpation of the painful areas elicits tenderness.

Occasionally, during decompression, the eustachian tube may become blocked and produce an excruciating type of pain localized in the middle ear as the tympanic membrane is pushed outward by the relative positive pressure in the tympanum. A similar obstruction of a sinal ostium during decompression, usually the frontal, likewise elicits pain which, however, is diffuse, dull, and aching in character in contrast with the lancinating or burning pain associated with negative pressure in the sinus.

The etiology of pain associated with relative positive pressure in sinal spaces

is probably related to compression of the lining membrane against the osseous wall of the sinus. On a wholly different basis, however, is the pain incident to relative negative pressure within a sinus which may arise, in part, from vascular distension and be mediated through the sensory nerves running in periarterial sympathetic plexuses. In decompression sickness, for example, air bubbles may distend pulmonary blood vessels as demonstrated by Gersh.[8] Such distended vessels when present in the lungs may give rise to the condition of "chokes" which affects not only divers but aviators as well. It has been observed that deep breathing which would tend, by reason of increased negative intrathoracic pressure, to augment vascular distension, elicits the presence of early or otherwise unrecognized "chokes."[2]

These observations, in summary, indicate that relative negative pressure of small magnitude within occluded spaces gives rise to a cupping action, brings about vascular distension, congestion and hemorrhage, and is associated with pain restricted to, and designating, the area of involvement. Occasionally, a relative positive pressure in the sinuses produces a diffuse, poorly localized and "deep" type of somatic pain.

Oxyotitis media. — In 1940, divers making simulated altitude ascents to 38,000 feet returned to ground level entirely free from objective or subjective aural symptoms. During the night or upon awakening the following morning, complaints were made of earache, a sensation of fullness and especially of fluid in the ears, and impaired hearing. Inspection of the tympanic membranes usually revealed changes similar to those found in the early stages of aero-otitis media.[3]

In the spring of 1942, similar complaints were made by engineers engaged in repeated high altitude flights. The symptoms were, at times, sufficiently severe to produce disability.

The explanation of the puzzling interval of well being followed by delayed symptoms incident to sleep is attributed to a negative pressure effect brought about by the absorption of oxygen from the middle ear spaces during sleep when conscious opening of the eustachian tubes is suppressed. In ascent to 38,000 feet, for example, four-fifths of the air originally present leaves the middle ear. During descent to ground level *if oxygen is inhaled during the whole period,* the middle ear becomes filled with oxygen in high concentration. The pressure of oxygen in the tympanum is of the order of 600 mm. Hg. while the tissue oxygen pressure may be less than 40 mm. Hg. The utilization of oxygen by the tissues results in a pressure gradient which tends to exhaust the oxygen from the tympanic space and to produce a cupping effect on the membranous lining. The diffusion of nitrogen out of the tissues apparently is too slow to compensate for the oxygen loss. A possible local irritative action of oxygen has not been evaluated.

The familiar "vacuum" frontal headache and the changes induced by the absorption of oxygen in complete tubal obstruction have the same etiologic basis.

The fact that relative negative pressure in the middle ear spaces can give rise to pain over the mastoid region and tenderness when the painful area is palpated emphasizes the need to consider the possibility of a type of mastoiditis caused by obstruction rather than infection. This consideration is applicable clinically to cases of catarrhal otitis media especially in children in whom the more abundant epipharyngeal lymphoid tissue might obstruct the auditory tube to produce an "aero-mastoiditis."

The following values are representative of gas pressures in tissues and in ventilated sinal and aural cavities:

	Gas Pressures in Sinal and Aural Cavities (mm. Hg.)		*Gas Pressures in Tissues (mm. Hg.)*
Nitrogen	563	←	573
Oxygen	150	→	40
Carbon dioxide	—	←	47
Water vapor	47		47
	760	→	707

Following occlusion of a sinal ostium, the pressure tends to decrease to 707 mm. Hg. Since the pressure in the blood vessels is 760 mm. Hg. plus capillary pressure, the blood vessels begin to dilate as soon as the absorption of oxygen in the occluded space results in a fall off of pressure from 760 mm. Hg. Measurements of the order of - 25 mm. Hg. were obtained by Van Dishoeck[15] and attributed to oxygen resorption from the tympanum.

This type of injury can be avoided by breathing *air* during descent beginning at an altitude of 15,000 feet. In the comprehensive studies of Bowen,[6] air inhaled at still higher levels during descent was even more effective.

Effect of pressure variations and trauma on hearing. — Confusion exists with reference to impairment of hearing induced by pressure trauma. Following acute trauma, the audiogram reflects diminished perception of sound over the whole frequency range. As the pathologic disturbance undergoes resolution, however, hearing returns to the initial level of acuity. The rarity or absence of proved cases of deafness arising from injury incident to pressure trauma in deep sea diving or caisson work stands in contrast to proved cases of permanent deafness caused by gunfire.

Heller, Mager and von Schrötter stress the fact that permanent deafness from compression injury did not occur. These authors clearly distinguish between compression injury of the tympanum and labyrinthine vertigo and deafness which occurred occasionally (14 cases in 675 workers) and was thought to be due to interference with the blood supply to the cochlea by nitrogen bubbles. This concept is supported by the delayed appearance of symptoms following decompression, their rapid, spontaneous disappearance at times or during recompression, the frequent absence of changes in the middle ear, and the fact that these symptoms never occurred during compression.

Two cases of permanent deafness, however, have been reported by Simpson[13] in Royal Air Force aviators following rapid descent incident to dive bombing. McGibbon,[11] in a study of 100 aviator patients with symptoms referable to the ear due to too rapid compression, reported that although deafness was the most common complaint, not one in the series manifested a permanent "inner-ear" type of deafness mentioned by Simpson.

Of definite importance is the matter of possible injury to the labyrinth. Heller, Mager and von Schrötter cite the measurements by Politzer and Bezold, which indicate that decrease in labyrinthine pressure accompanied the decrease of relative pressure in the tympanum. They believed that stasis, transudation and hemorrhage occurred in the labyrinth as well as in the middle ear cleft.[10] In the absence of permanent deafness, however, it does not appear probable that such destructive changes affect the labyrinth. It should rather be expected that the pressure in the labyrinth will equal or closely approximate that of the cerebrospinal fluid which attains equilibrium with variations in ambient pressure without a lag. Under these conditions, the integrity of labyrinthine structure would seem to depend upon the resistance of the round win-

dow to any relative negative pressure existing in the tympanum.

In three dogs subjected to rapid compression, Vail[14] found that although the tympanum was severely injured, there were no appreciable alterations in the labyrinth. Additional studies are required to settle this problem.

With respect to deep sea divers subjected to varying degrees of pressure trauma, usually of mild degree over a period of five to fifteen years, audiograms indicate that the loss of hearing at 4096 double vibrations is consistent with the average loss for a similar control group.

An impressive fact, however, is the paucity of cases of permanent deafness attributable to barotrauma not only in deep sea diving but in aviation as well.

Incidence of aero-otitis media and aero-sinusitis. — The incidence of aero-otitis is primarily related to the degree of tubal obstruction and the rate at which the compressive force is applied. The structure of the eustachian tube makes it peculiarly susceptible to obstruction. The vascular mucosa, filled with mucin-secreting goblet cells and supported by a rich vascular and glandular bed containing lymphatic tissue, lines a firm cartilaginous tube, which easily becomes sealed by edema, cellular infiltration and mucus. The presence of lymphoid tissue around and within the opening of the eustachian tube acts as a potential seal. It is not surprising, therefore, that infection, allergic reaction and such mild trauma as that induced by negative pressure, singly or in combination, produce frequent obstruction.[9,12]

The factor of trauma arising from negative pressure is better appreciated when one considers the fact that on successive exposures to changes in pressure, equalization of pressure on the two sides of the tympanic membrane may become more difficult due to congestion and edema produced by repeated efforts to "clear the ears."

The degree of tubal obstruction depends mainly, however, upon the presence and severity of infection in the nasopharynx. "Colds" represent the most common type of infection causing this disability. It is not surprising, therefore, that the incidence of barotrauma varies from 5 to 20 per cent in diving and flight operations. In 1932, out of 453 submarine personnel, 11.5 per cent were unable to equalize 50 pounds per square inch pressure applied in a chamber during a period of 5 to 10 minutes because of tubal blockage. One-half of 1 per cent of the men suffered from sinal blockage. In 1936, out of 1748 submarine personnel, 8 per cent subjected to the same pressure test were disqualified because of tubal blockage.[4] In a pressure chamber test for student divers, 60 men out of 326 failed on their first attempt due to colds but only 8 of the group were permanently disqualified.

Value of a pressure chamber as a means of diagnosis. — During the past fourteen years pressures of 5 to 50 pounds per square inch applied to candidates for the submarine escape drill and deep sea diving have demonstrated the value of the pressure chamber as a means of diagnosis of aural and sinal blockage. Its obvious advantages consist chiefly in the ability to apply a wide range of pressures at a controlled rate to one or more individuals.

In the Navy, it has served to indicate the prevalence of nasopharyngeal infection which ordinarily would not exclude individuals from duty. Men, excepting those with patulous membranes, who can accommodate pressure at the rate of 45 pounds per square inch per minute are found to be comparatively free of nasopharyngeal infection. Some 30 to 50 per cent of a group of apparently healthy individuals may be expected to fail

this test at any given time. If the rate of compression is extended over a period of five minutes, then from 5 to 20 per cent of a similar group of men would fail the test.

The degree of tubal obstruction is reflected quantitatively in the rate of tolerance to increased pressure. An individual with a cold may require a period of thirty minutes to accommodate to an excess pressure of 5 pounds per square inch. The empirical data point to a high correlation between acute nasopharyngeal infection and tubal obstruction. The relationship between subclinical infection of the pharynx and tubal blockage merits further study.

Therapy.—Conservative treatment of the "cupping effect" by means of nontraumatizing ventilation and drainage can be carried out by the application of controlled pressure at a rate tolerated by the patient. Both inspection of the tympanic membrane and discomfort serve to protect against injury from too rapid application of pressure. The release of ambient pressure after it has been raised to 5 or 10 pounds per square inch will serve to effect drainage without trauma since intra-aural or intrasinal pressure cannot then become negative.

The following statements outline the responses of patients subjected to pressure and illustrate principles underlying diagnosis and therapy.[5]

1. The complaint was that of headache over the eyes and eyestrain. In the middle meatus of each nostril, polyps were present. The pressure after being raised to 10 pounds per square inch in the compression chamber was rapidly released. Inspection of the left meatus during the release of pressure revealed a bubbling out of air and secretion from beneath the polypi.
2. Pain, intensified by bending over, was present over the eyes. Errors of refraction were not found. The nasal septum was deviated to the left and touched the middle turbinate. Purulent secretion was present. Tympanic membranes appeared normal. Following the slow application of pressure, pain disappeared. Upon release of pressure, however, severe pain developed over the eyes. Again the pressure was raised to 15 pounds and the pain was relieved only to return when the pressure was released. An astringent was then applied to the nasal mucous membranes. Purulent secretion and air bubbles were observed to exude from the opening of the frontonasal duct accompanied by a swishing sound. With the equalization of pressure, pain was relieved.

   Comment: This case illustrates the relation of symptoms to inequality of pressure. Excess intrasinal pressure either higher or lower than tissue pressure was associated with pain.
3. Frontal pain on bending over, malaise and nasal congestion were present. Pressure was raised to 2 pounds and was accompanied by intense, lancinating, multiple stimuli pain in the left eyebrow and nostril which slowly subsided. Pressure was raised to 5 pounds and then decreased slowly. The release of pressure was accompanied by serous drainage. On successive days the pressure was gradually increased. With the subsidence of infection, the usual rate of pressure increase was accommodated.
4. Patient had head cold with malaise, nasal congestion, and frontal pain on lowering the head. Pressure was raised to 2 pounds in the chamber. Intense, lancinating pain was felt over the left eyebrow and in the left nostril. The pain slowly subsided as the pressure was equalized. The pressure was raised to 5 pounds and then decreased slowly to produce a small amount of serous drainage.

The next day the pressure was raised to 7 pounds. Intense pain was experienced over the left eye and bridge of the nose at 3, 5, and 7 pounds pressure. Upon rapid release of pressure, a bloody, purulent discharge was obtained from the left nostril.

Comment: The rapid application of pressure purposely applied induced hemorrhage into the sinus. Slow application of pressure would have prevented injury.

5. The complaint was that of earache. Examination of the left ear revealed inflammatory changes involving the tympanic membrane. A positive pressure of 4 pounds was applied slowly in the compression and was accompanied by a dull aching pain in the left ear. Following release of pressure, the patient stated that, "something busted in the left ear and my throat filled up with something warm, like fluid that made me swallow. This was accompanied by a whistling sound."

Comment: Drainage of the middle ear appears to have taken place through the auditory tube.

6. In a case of drainage otitis media following paracentesis, pressure was raised to 5 pounds per square inch. Upon the release of pressure, drainage occurred through the incision.

These outline statements present the principle of securing effective drainage without trauma. The value of the principle of securing aeration and drainage by the employment of a chamber is being evaluated by such studies as Dr. Ivy and his coworkers[15] have been conducting over a period of several years.

Possibility of air borne dissemination of infectious material. — Complications involving the ear and sinuses appear to be no more prevalent following pressure trauma, if immersion of the head in water is avoided, than they are in individuals not subjected to compression. A factor limiting complications may be the difficulty experienced in equalizing pressure when even mild degrees of nasopharyngeal infection are present. The thoroughness, however, of aeration of the aural and sinal spaces in diving and aviation gives ample opportunity of the dissemination of infectious material. It would appear then that such mode of infection must be unusual.

Concluding remarks. — At the present time, the experience gained by physicians working in low pressure chambers and through the extensive development of aviation has resulted in increased appreciation of the usefulness and limitations of the pressure chamber. Its use as a diagnostic agent constitutes its chief value in the field of otolaryngology. The therapeutic value appears to be an adjunct to other forms of treatment by securing nontraumatizing and effective ventilation and drainage. The curative value is restricted to its efficacy in ventilating and draining the sinal and aural cavities.

With reference to the traumatic effect produced by differences in pressure, prime considerations are:

1. the frequent appearance of apparently extensive injury to the structure of the middle ear,
2. the spontaneous resolution of these changes *without treatment,* and
3. the absence of complications.

It is on the basis of these considerations that specially adapted pressure chambers may be employed by the otolaryngologist with safety not only as an aid in diagnosis but to promote ventilation and drainage of aural and sinal spaces.

ACKNOWLEDGMENT

I am indebted to Lt. Comdr. W. A. White, Jr. (M.C.), U. S. Navy, and Lt. Robert Hayter (M.C.), U. S. Navy, for obtaining the data shown in figures 1 and 2.

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TABLE 1

Rate of Accommodation of the Aural and Sinal Spaces to Increased Pressure

Diving Operations

Breathing Medium	*No. of Dives*	*Depth (feet)*	*Pressure (gage)*		*Time (min.)*		*Remarks*
			psi	*mm. Hg.*	*Total*	*Range*	
Air	301	125	56	2879	4.7	1-17	Student divers
Air	400	225	100	5182	5.2	2-14	(Wet tank)
He-O_2	400	225	100	5182	4.6	2-15	Open sea
He-O_2	145	225 to 240	100 to 107	5182 to 5527	3.7	2-7	(USS SQUALUS)

Altitude Descent

Breathing Medium	*Simulated Altitude*	*Pressure (mm. Hg)*	*Time Required (seconds)*
O_2	48,000 to 12,000	96 to 483	10
"	45,000 to 15,000	111 to 429	30
"	45,000 to 12,000	111 to 483	45
"	41,000 to 10,000	134 to 523	78
"	40,000 to 10,000	141 to 523	6
"	40,000 to sea level	141 to 760	37
"	40,000 to sea level	141 to 760	50

TABLE 2

Pressure differences (mm. Hg) at which equalization of pressure was effected by swallowing when the barometric pressure was uniformly raised from 760 to 3020 mm. Hg (1 to 4 atmospheres) in 8 minutes.

Air Inhalation				*Helium-Oxygen Inhalation*		
1 to 2 atm.	2 to 3 atm.	3 to 4 atm.		1 to 2 atm.	2 to 3 atm.	3 to 4 atm.
91	91	104		61	110	112
81	89	102		62	94	111
51	76	98		71	89	109
76	99	127		107	99	132
81	97	105		71	88	102
81	100	137		99	107	75
82	86	107		76	107	104
93	130			79	99	
86				89		
Av. 80.2	96	111.4		79.3	99.1	106.4

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Postural equilibrium and vestibular response at 49.5 ATA

W. R. BRAITHWAITE, T. E. BERGHAGE, and J. C. CROTHERS

U.S. Navy Experimental Diving Unit, Washington Navy Yard, Washington, D.C. 20374

Braithwaite, W. R., T. E. Berghage, and J. C. Crothers. 1974. Postural equilibrium and vestibular response at 49.5 ATA. Undersea Biomed. Res. 1(4):309-323.–In response to the relatively high incidence of vestibular symptoms reported during deep experimental saturation dives, the U.S. Navy included measures of postural equilibrium and vestibular function in its 1600-fsw chamber dive protocol. Six subjects were pressurized in 6 days to 49.48 ATA. After spending 7 days at this pressure, they were decompressed in 19 days to the surface. The tests administered prior to, during, and following the dive included electronystagmography with mental alerting, pendulum tracking, optokinetic stimulation, cold caloric stimulation, and positional testing, along with three balance rail tests and two statometer tests. During the dive all of the measures of vestibular function stayed within normal limits; the tests of standing steadiness all showed statistically significant deviations from surface values. Performance on both the balance rail and the statometer showed a striking deterioration associated with increased pressure and some adaptation with time at depth. The decrements observed were very complex in nature with statistically significant interactions among all of the experimental variables. Experimental variables in the study included ambient pressure, individual differences, time at 1600 fsw, dive phase (compression versus decompression), and, in the case of the statometer, response frequency.

vestibular response
performance
helium
nervous system
saturation diving

The maintenance of human postural equilibrium involves the complex interaction of visual, vestibular, and proprioceptive inputs with voluntary and reflex CNS responses through peripheral nerves to the skeletal musculature. Each of the factors or pathways involved is a complex system in itself and a disturbance of any of them can cause partial or complete loss of this equilibrium. Almost from the very first exposures of man to hyperbaric environments disturbances in vestibular system functioning have been reported. Excellent reviews of this literature as related to diving have been done by Lundgren (1965), Terry and Dennison (1966), Vorosmarti and Bradley (1970), Rubenstein and Summitt (1971), Kennedy (1972), and Edmonds, Freeman, Thomas, Tonkin, and Blackwood (1973).

Symptoms elicited by vestibular dysfunction include nausea, vomiting, vertigo, ataxia, nystagmus, disorientation, pallor, sweating, drowsiness, and salivation. Because the reported systems vary considerably, Edmonds et al. (1973) have developed a classification system for their etiology. One of these classifications, entitled *unequal vestibular response due to abnormal gas pressure,* contains symptoms caused by breathing various gases under high pressure. High partial pressures of nitrogen, helium, oxygen, and carbon dioxide have all

been associated with central nervous system (CNS) effects causing vestibular symptoms. This relatively new class of symptoms has gained importance with the advent of deep saturation dives using synthetic gas mixtures. In 1965 the British conducted chamber dives to depths of 600 to 800 fsw. Experimental subjects on these dives suffered from whole body tremor and vertigo (Hunter and Bennett 1974). Compression rates on these dives were quite rapid, however, and the effects of pressure changes could not be ruled out.

The French have also observed complex CNS symptoms on their series of deep chamber saturation dives. In 1968 Brauer termed this response to high pressure the *high pressure nervous syndrome* (HPNS), describing it as a grouping of clinical and electroencephalographic manifestations that characterize the CNS disorders evoked by the passage to and stay under high pressures while breathing various gaseous mixtures. Brauer went on to indicate that as depths beyond 30 ATA are reached, an individual's neuromuscular performance will be increasingly impaired and by 33 ATA, this syndrome will increasingly hinder the individual's activities. The deep chamber dives that have been made since this projection have confirmed the changes in neuromuscular response and pointed up the importance of this syndrome for vestibular system functioning. Edmonds et al. (1973) indicate that the HPNS vestibular system involvement is virtually untouched by medical practitioners knowledgeable in the field of otology.

In response to the relatively high incidence of such dysfunction during deep experimental saturation dives, the U.S. Navy included several measures of postural equilibrium and vestibular system functioning in its 1600-fsw (49.5 ATA) chamber dive protocol. The study reported here was designed to quantify these responses at several depths and determine their functional relationship to pressure.

PROCEDURE

RATIONALE

This study was part of a coordinated dive program jointly undertaken by the Navy Experimental Diving Unit, the Naval Medical Research Institute, and the Bureau of Medicine and Surgery. The 1600-fsw (49.5 ATA) chamber dive during which these data were gathered culminated a series of chamber exposures that extended over a 12-month period. This series of biomedical and equipment evaluation dives was designed to document the diver's ability to perform useful physical work in the water using U.S. Navy underwater breathing apparatus. To perform these dives safely, extensive neurophysiological and cardiorespiratory monitoring was done in addition to a rather heavy schedule of equipment evaluation tests. It is within these operational and time constraints that tests had to be designed to study the problems of postural equilibrium and vestibular dysfunction.

Two tests were designed to detect any disturbances of postural equilibrium or vestibular function. A standard ataxia rail battery (Graybiel and Fregly 1965) was selected to monitor standing steadiness. Electronystagmography (ENG) monitoring for spontaneous nystagmus was implemented as a sensitive detector of vestibular imbalance. A more complete test battery was developed to gather data on any disturbances found. The additional tests were given to help define or locate the problem.

The complete vestibular battery contained four additional tests. A cold caloric test of vestibular end organ function was selected because it was easier to perform and assured a more consistent thermal stimulus than could be achieved by other methods in the highly heat-conductive helium atmosphere. Optokinetic (OPK) stimulation of nystagmus tested the visual and CNS components of the reflex; pendulum-following tested higher level voluntary

muscular control and demonstrated any latent spontaneous or gaze nystagmus induced by lateral gaze deviations. Positional testing was used to detect and rule out any positionally dependent nystagmus.

Statometer tests were used to provide frequencies and amplitudes of postural corrections. Since the balance rail tests detected significant disturbances of postural equilibrium early in the series of workup dives, the statometer tests were scheduled by protocol to monitor these disturbances throughout the dive.

PROTOCOL

The complete test battery was scheduled predive, at maximum depth, and postdive to provide baselines and assure that the subjects had normal vestibular function before, during, and after this dive even if they were asymptomatic. The balance rail tests, statometer tests, and ENG testing for spontaneous nystagmus during audiograms were performed during the stops at 400, 1000, and 1300 fsw (see dive profile, Fig. 1). The statometer tests were also

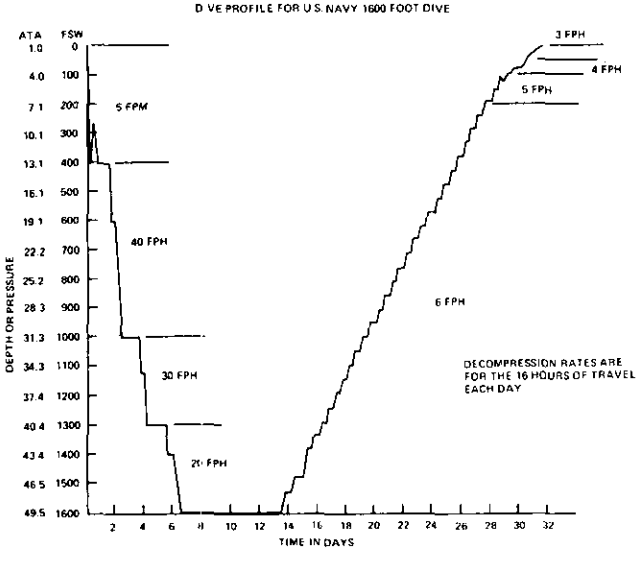

Fig. 1. U.S. Navy 1600-fsw dive profile.

done at the 600- and 800-fsw levels. While at 1600 fsw, all monitor tests were done during the first, third, and sixth days at depth. The balance rail tests were performed every day during decompression, ENG's were done every other day, and statometer tests were conducted at specific depths: 1300, 1000, 800, 600, and 400 fsw.

ELECTRONYSTAGMOGRAPHY

The full vestibular cerebellar diagnostic procedure took about 60 min/subject. The step-by-step procedure used is outlined below:

1. Electronystagmographic potentials were picked up by surface electrodes applied to the oil-free abraded skin at the outer canthus of each eye with a conductive paste. A ground reference electrode was applied just above the bridge of the nose. The signal was amplified by a differential-input DC channel on a Grass polygraph. Since direct DC recording proved

to be too unstable for lengthy monitoring in this environment, the longest AC half-time available was used: TC = 0.8. This proved to be a very stable, satisfactory recording mode. The recording polarity was set so that eye deflection to the left caused pen deflection to the bottom of the chart and the chart speed was set at 15 mm/sec. Deflection was calibrated at 1° eye deflection per mm pen deflection on the chart by having the subject place his head in a headrest located 17 inches from a box with small lights 3 inches apart and then shift his gaze from light to light as they were selected by the investigator calibrating the recorder.

2. In the test for spontaneous nystagmus, the subject sat erect with his eyes closed, staring straight ahead, and performing mental arithmetic aloud. Recordings were taken in the same way with the subject lying flat on his back, then on his right and left sides.

3. During the OPK test, the subject sat erect with his eyes open. He stared at a projection screen on which OPK stimulus lines were moved first to the left and then to the right at various speeds between 30° and 40°/sec. The subjects were tested first with the right eye covered and then with the left eye covered.

4. For the pendulum-follow test, the subjects, while sitting erect, had to follow visually a swinging pendulum (a ball on a string). The pendulum was positioned 20 inches in front of the subject's nose; it swung back and forth through a 24-inch arc. As with the OPK test, both eyes were evaluated separately. Although the frequency (0.7 Hz) and initial gaze angles (30°) were close to the limits at which normals begin to have difficulty, all subjects tested produced a normal sine wave ENG on pendulum-following.

5. Prior to the cold caloric test, the ENG electrodes were again calibrated with the subject in the caloric test position (CTP). (In the CTP, the subject lies flat on his back with his head supported at about a 30° angle such that the line passing through the outer canthus of his eye and the tragus of his ear is vertical.) The subject was monitored in this position for spontaneous nystagmus, after which 5 cc of ice water were injected into his left ear. During this procedure, the subject remained still, with his eyes closed, and performed mental arithmetic. The ENG was recorded for 3 min. During the last minute of nystagmus, the subject opened his eyes to test for the obliteration of nystagmus by visual fixation. Following this, the subject rested for 7 min. The test was then repeated for the right ear.

The ENG monitoring for spontaneous nystagmus was done during conduction of an audiogram that served as the mental alerting task during the test. Electronystagmographic electrodes were applied as described in step 1 above and an audiogram was performed by the subject who sat erect and kept his eyes closed. The ENG was recorded for at least 1 min during the testing of each ear.

BALANCE RAIL

Balance rail apparatus and tests were derived from the short version of a well-documented quantitative ataxia test battery developed by Graybiel and Fregly (1965) and Fregly, Smith, and Graybiel (1972). As shown in Fig. 2, the tests involve two different rails. The wide rail is 2¼ inches (5.7 cm) wide and the narrow rail is ¾ inch (1.9 cm) wide. Graybiel's standard battery involved three tests: standing on the wide rail eyes closed, standing on the narrow rail eyes open, and walking heel-to-toe on the narrow rail. The first two of these were used in standard form, but the walking test was dropped during previous dives because it was the least consistent, required a great deal more room than was available, and was considered relatively unsafe inside the cramped hyperbaric quarters. Previous dives also had pointed out that at some depth the two standing tests could not be performed at all by some divers. In other words, diving could make normal subjects more ataxic than these two tests could

Fig. 2. Subject standing on the balance rail.

measure. Therefore, a third test, standing on the wide rail with eyes open, was added. Since all subjects could get perfect scores on this test, it was insensitive near the surface, but as the subject's balance deteriorated it could provide a measure still sensitive to gross abnormality. This is a standard test in the long version of Graybiel's test battery.

In each of the three tests, the subject stood on the appropriate rail with his feet aligned with the rail in a heel-to-toe position and his arms folded across his chest. Five trials (not including false starts) on each test were timed until the subject fell or removed his feet from position on the rail. Prior to the dive, each of the subjects had practiced these tests many times and the tests were performed at least once daily in the week before the dive, so that the effect of learning would be minimal.

STATOMETER

The statometer (Fig. 3) is constructed by suspending a rigid piece of plywood from a rigid metal frame by four strain-gauge bolts. These gauges are connected electrically into two

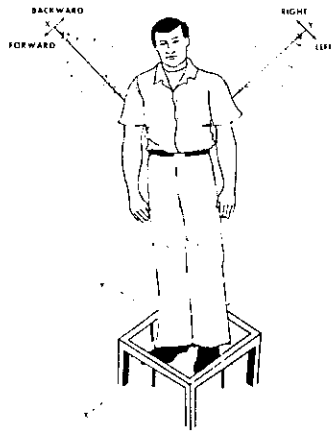

Fig. 3. Subject standing on the EDU statometer.

Wheatstone bridges which are sensitive to changes in weight along the lateral and sagittal axes but not along the vertical axis. The bridges were powered and the output signals recorded by a Grass polygraph outside the chamber. The analog signals were also recorded on magnetic tape for later analysis.

The testing was conducted in the "wetpot" portion of the chamber complex where each subject positioned himself on the statometer plate. After he was stable and visually fixating on a spot on the chamber wall, he reported to the experimenter outside the chamber that he was ready. The experimenter indicated to the subject when he was starting the recordings, and from that point on, the subject was to stand as steady as possible for 2 min. Following this sample, the subject was told to shut his eyes and stand as steady as possible for an additional 2 min. After this second sample, the subject carefully stepped off the plate.

ANALYSIS

A randomized block factorial analysis of variance (ANOVA) was used in assessing the statistical significance of the balance rail times and the statometer amplitude scores. The statometer analog signals that were recorded on magnetic tape during the dive were digitized and analyzed on a PDP-12/40 computer using a frequency analysis program developed at the Naval Medical Research Institute.

RESULTS

Subjectively, the subjects did not report any vestibular symptoms or difficulty with balance until deeper than 1000 fsw, although some intention tremor and associated difficulty with fine manual tasks was present before that depth. Below 1000 fsw, there was subjective impairment of balance to varying degrees, but no vestibular symptoms were reported.

ELECTRONYSTAGMOGRAPHY

For purposes of understanding, we define *nystagmus* as a regular sawtooth ENG recording with at least 3 peaks whose direction is defined by the direction of the fast component and whose amplitude is determined by the slope of the slow component in degrees/sec. Normally one does not expect spontaneous nystagmus in any position or at any gaze deviation less than 20°. Cold caloric stimulation should produce a bilaterally symmetrical nystagmus in the direction toward the stimulated ear, which begins 20-30 sec after water instillation, lasts 2-2½ min, is mostly obliterated by visual fixation in the last minute, and should not change significantly in amplitude (slope of slow component) from test to test.

At no time during the dive was any spontaneous nystagmus observed. Nystagmus induced by optokinetic and cold caloric stimulation was always within normal limits, although slightly diminished in amplitude at depth.

BALANCE RAIL

The results of the analysis of variance for the three balance rail tests are shown in Table 1. The variable, called "blocks" in Table 1, is the difference between trials during the various test periods. It is the only variable that is not statistically significant. Differences between the three tests, the subjects, the various depths (pressures), and compression-decompression were all statistically significant at the $P < .001$ level or better. In addition, all of the

TABLE 1

Analysis of variance summary table of balance rail results from the U.S. Navy 1600-fsw dive

Source	SS	df	MS	F
Blocks	115	2	57.5	1.70*
Treatments				
T (Tests)	277250	2	138625.0	4099.43
S (Individual Differences)	2199	5	439.8	13.01
D (Depth)	1234	4	308.5	9.12
P (Phase–Compression-Decompression)	468	1	468.0	13.83
TS	1593	10	159.3	4.71
TD	4633	8	579.1	17.13
TP	303	2	151.5	4.48
SD	3143	20	157.2	4.65
SP	955	5	191.0	5.65
DP	9305	4	2326.3	68.78
TSD	4319	40	108.0	3.19
TSP	1732	10	173.2	5.12
TDP	4183	8	522.9	15.46
SDP	1635	20	81.8	2.42
TSDP	5273	40	131.8	3.90
Residual	12106	358	33.8	
Total	330446	539		

* Value not reaching statistical significance. All other values are significant at $P < .001$.

interactions between these variables were significant. To summarize this table, one would have to say that each subject's performance was statistically different on each test, at each depth, and during each phase of the dive (compression-decompression).

A graphical presentation of the results is shown in Fig. 4. As can be seen, the results of all three tests have different profiles indicating differences in test sensitivity. The test results have an upper limit of 180 sec, a perfect score, and a lower limit of about 10 sec, the length of time a subject can stay in position regardless of his balancing capability. As shown by the decrease in variation (standard error of the mean) as test results approach these limits, the tests are not sensitive or responsive. For this reason, these three tests can only be considered in the region for which they are sensitive. The Narrow Rail Eyes Open (NREO) and Wide Rail Eyes Closed (WREC) tests are sensitive from the surface to about 1000 and 1300 fsw, respectively. The Wide Rail Eyes Open (WREO) test becomes sensitive at about 1000 fsw and continues to be so to the greatest depth of this dive.

STATOMETER

The analysis of variance results for the statometer test of equilibrium are shown in Table 2. Blocking across samples was done to remove the variance among samples from the error term. The experimental variables of interest are the frequency, whether the subject's eyes were open or closed, the individual differences, depth (pressure), and the dive phase (compression-decompression). Of these five experimental variables, only one, the dive phase, is not statistically significant. As with the balance rail test, most of the interactions among experimental variables are also significant, indicating a very complex phenomenon.

A graphical presentation of the results are shown in Figs. 5, 6, and 7. In Fig. 5, changes in signal amplitude are depicted. The most dramatic change occurs between 1000 fsw (31.3

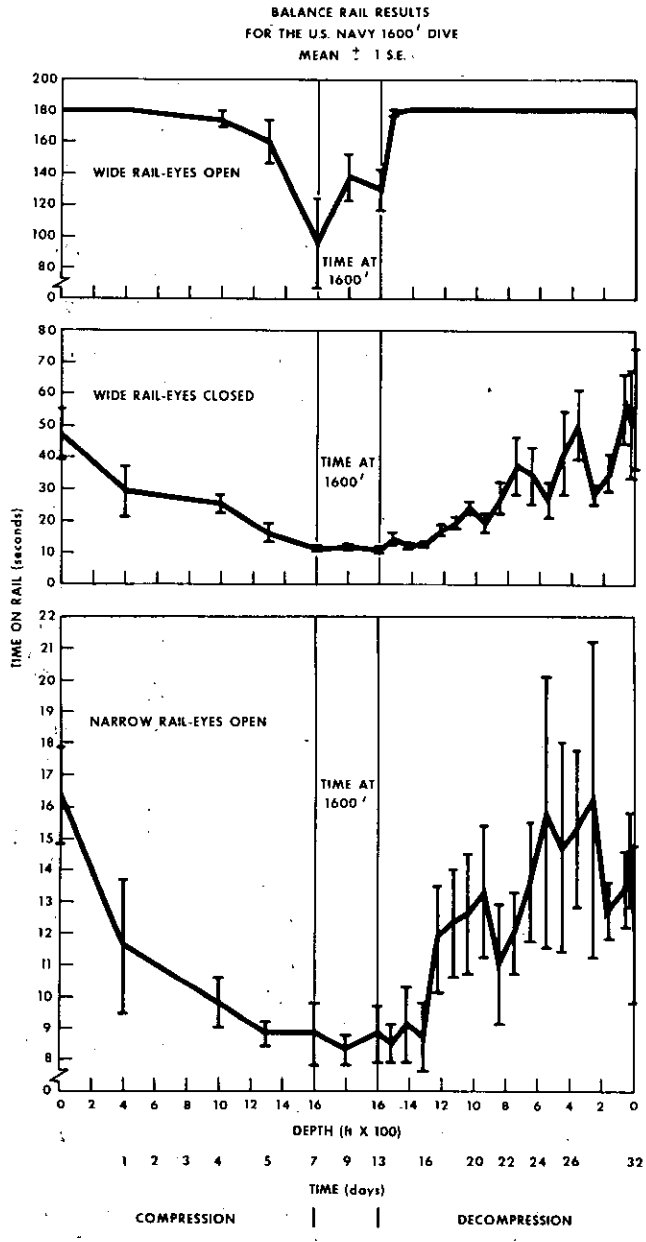

Fig. 4. Balance rail results for the U.S. Navy 1600-fsw dive.

ATA) and 1300 fsw (40.4 ATA). Between these depths, there is a significant increase in signal amplitude and an impressive change in the variability among individuals.

Figures 6 and 7 present the statometer frequency analysis results. An inspection of these figures reveals two consistent, rather obvious findings. The first is the rather marked shift in the frequency distribution between 1000 fsw (31.3 ATA) and 1300 fsw (40.4 ATA). This finding was consistent for all individuals in both the eyes-open and eyes-closed conditions.

TABLE 2

Analysis of variance summary table of statometer results from the U.S. Navy 1600-fsw dive

Source	SS	df	MS	F
Blocks	16344	1	16344	5.93
Treatments				
F (Frequency)	1052513	3	350837.7	127.32
E (Eyes Open or Closed)	197152	1	197152.0	71.55
S (Individual Differences)	299690	5	59938.0	21.75
D (Depth)	295751	5	59150.2	21.47
P (Phase–Compression-Decompression)	5118	1	5118.0	1.86*
FE	357406	3	119135.3	43.23
FS	388031	15	25868.7	9.39
FD	430839	15	28722.6	10.42
FP	1640	3	546.7	.20*
ES	200027	5	40005.4	14.52
ED	164822	5	32964.4	11.96
EP	1580	1	1580.0	.57*
SD	408638	25	16345.5	5.93
SP	14614	5	2922.8	1.06*
DP	84985	5	16997.0	6.17
FES	245438	15	16362.5	5.94
FED	223494	15	14899.6	5.41
FEP	2672	3	890.7	.32*
FSD	493686	75	6582.5	2.39
FSP	47089	15	3139.3	1.14*
ESD	296709	25	11868.4	4.30
ESP	7772	5	1554.4	.56*
FDP	125081	15	8338.7	3.03
EDP	48136	5	9627.2	3.49
SDP	125879	25	5035.2	1.83
FESD	403005	75	5373.4	1.95
FESP	19821	15	1321.4	.48*
FEDP	59147	15	3943.1	1.43*
FSDP	200355	75	2671.4	.97*
ESDP	126615	25	5064.6	1.84
FESDP	207866	75	2771.6	1.01*
Residual	1584459	5755	2755.6	
Total	8136374	1151		

* Values not reaching statistical significance. All other values are significant at $P < .005$ or better.

The 0.4 Hz portion of the signal returns upon reaching the 1600-fsw (49.5 ATA) level. The second consistent finding in this analysis is the steady increase in the 0.4 Hz portion of the signal during decompression. The rise in this portion of the signal makes the pre- and postdive profiles look considerably different.

The analysis of variance performed on the statometer data from the three test periods at 1600 fsw to evaluate adaptation is summarized in Table 3. As with the two previous ANOVA tables, all of the main effects and most of the interactions are statistically significant.

The most important aspect of this table is the change in performance over time. Referring back to Figs. 4 and 5, one can see two and perhaps three indications that adaptation is

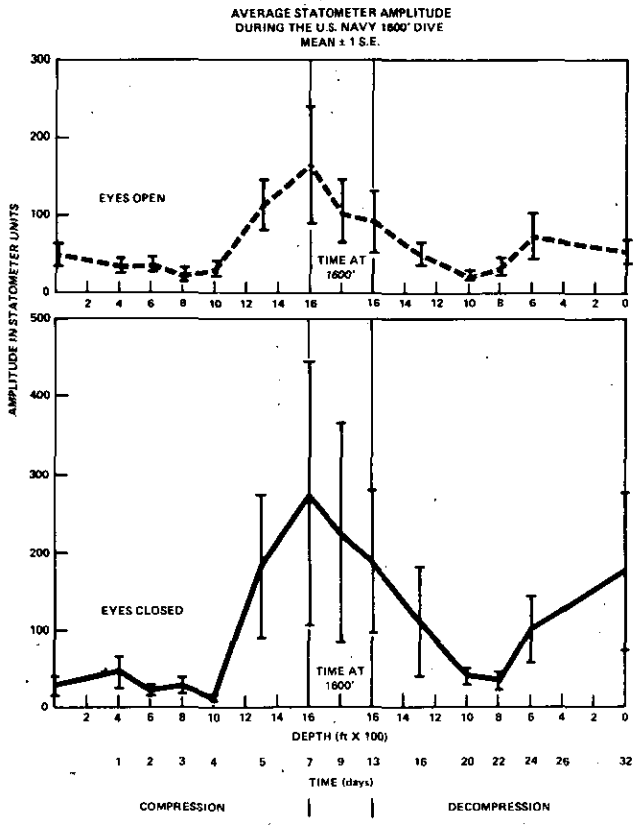

Fig. 5. Average statometer amplitude during the U.S. Navy 1600-fsw dive.

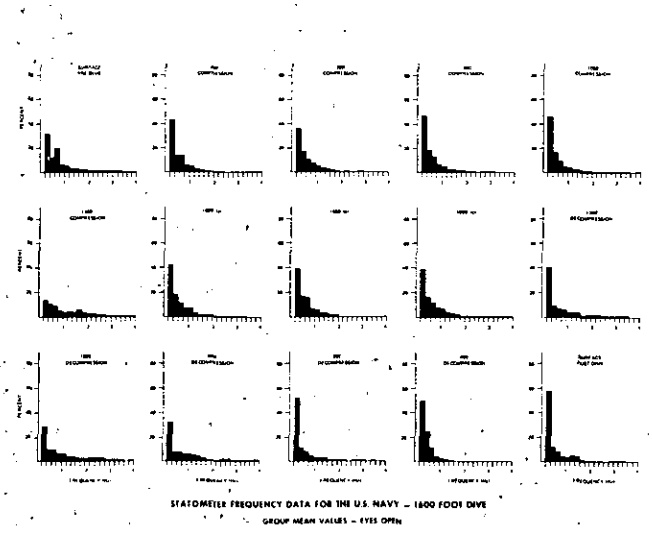

Fig. 6. Statometer frequency data for the U.S. Navy 1600-fsw dive: Group mean values–eyes open.

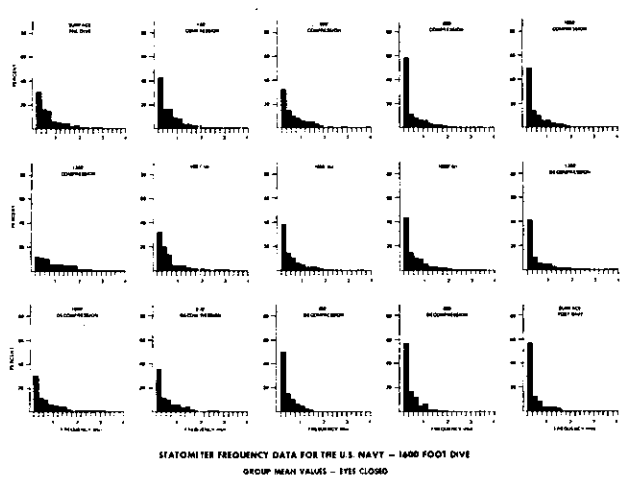

Fig. 7. Statometer frequency data for the U.S. Navy 1600-fsw dive: Group mean values–eyes closed.

TABLE 3

Analysis of variance summary table of adaptation while at 1600 fsw

Source	SS	df	MS	F
Blocks	39874	4	9968.5	7.88*
Treatments				
F (Frequency)	3089747	9	343305.2	271.47
E (Eyes Open or Closed)	252381	1	252381.0	199.57
FE	1321387	9	146820.8	116.10
S (Individual Differences)	479325	5	95865.0	75.81
FS	1936525	45	43033.9	34.03
ES	255079	5	51015.8	40.34
FES	947529	45	21056.2	16.65
T (Time)	20121	2	10060.5	7.96
FT	80926	18	4495.9	3.56
ET	26793	2	13396.5	10.59
ST	25703	10	2570.3	2.03*
FET	111673	18	6204.0	4.91
FST	131606	90	1462.3	1.16*
EST	205302	90	2281.1	1.80*
FEST	71777	90	797.5	.63*
Residual	1714847	1356	1264.6	
Total	10710594	1799		

* Values not reaching statistical significance. All other values are significant at $P < .001$ level.

taking place. First, there is a reduced amplitude for the statometer signal and an increased time on the wide rail with the eyes open. Second, the performance of the two balance testing devices for equivalent depths is better during decompression than during compression. This second observation holds true only for the initial portion of the decompression. A third possible indication of adaptation is the reduction in score variance over time. This third interpretation of the data is subject to criticism, however, in that the shifts in test score means are in the direction of reduced test sensitivity and, therefore, smaller score variation.

DISCUSSION

ELECTRONYSTAGMOGRAPHY

The results of the monitor and stimulation tests of visual, CNS, and labyrinthine function indicate that the subjects' originally "normal" vestibular system functions did not change significantly during the dive. Although the stimulation tests are rather gross and might not detect small changes, the monitor test for spontaneous nystagmus is acutely sensitive to changes that affect the left and right sides differently. Thus, the only changes in the vestibular system that would not be detected by these tests are small, overall distrubances which affect both sides equally. It is unlikely that the gross disturbance in balance seen on this dive can be explained by this type of small bilateral effect. Although these tests indicate

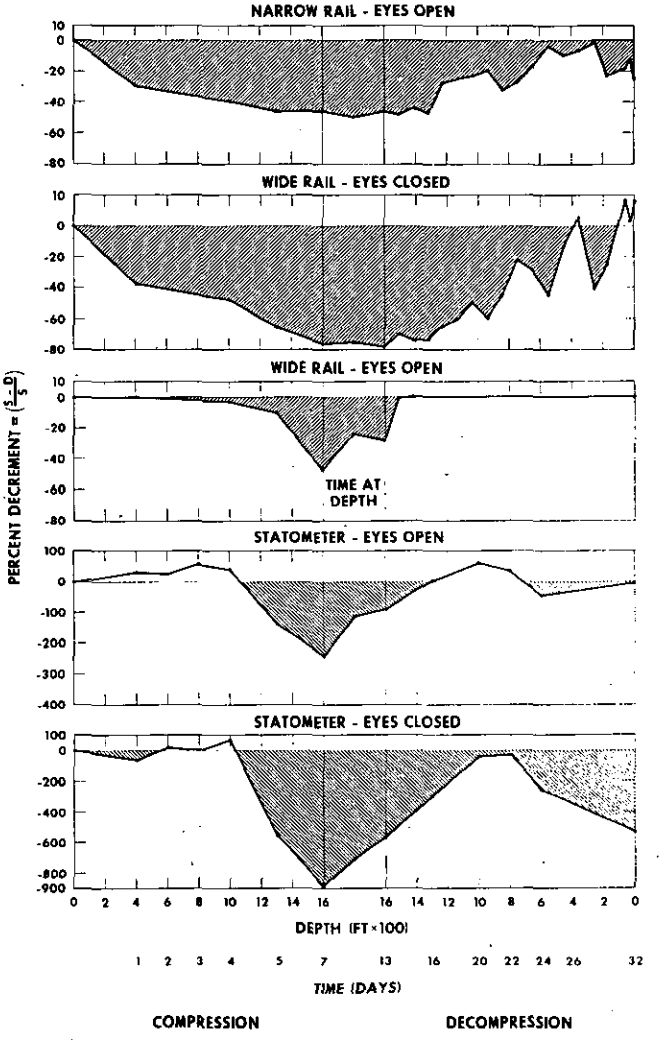

Fig. 8. Postural equilibrium results summary.

normal function of the visual, CNS, and labyrinthine portions of the vestibular reflex, they do not rule out severe dysfunction in the other parts of the balancing mechanism.

For purposes of comparing results, the five quantitative tests of postural equilibrium have been plotted in Fig. 8, using a common scale of percent decrement [(S – D)/S]. It is clear from this figure that postural equilibrium was greatly disturbed during this deep, helium-oxygen dive. We will look at the two groups of tests designed to help define this problem.

POSTURAL EQUILIBRIUM

Standing steadiness is a complex reflex process that involves the flow of impulses between the central nervous system and the muscular proprioceptors, skin exteroceptors, and the vestibular and visual apparatus. Impulses originating in the musculature of the feet and legs are the first kinesthetic cues of a postural equilibrium disturbance. These cues trigger reflex contractions in the muscle fibers. Because the deep pressure sensations habituate rather rapidly, either visual or labyrinthine information is necessary to provide drift stabilization.

Balance Rail. The balance rail results demonstrate a gross disturbance in the balancing mechanism which is related to depth and is especially severe below 1300 fsw (40.4 ATA). Since changing the width of the rail is analogous to changing the sensitivity control of any instrument, the results of the two eyes-open tests have been combined to yield the composite graph in Fig. 9. Since the actual sensitivity ratios for the rails have not yet been

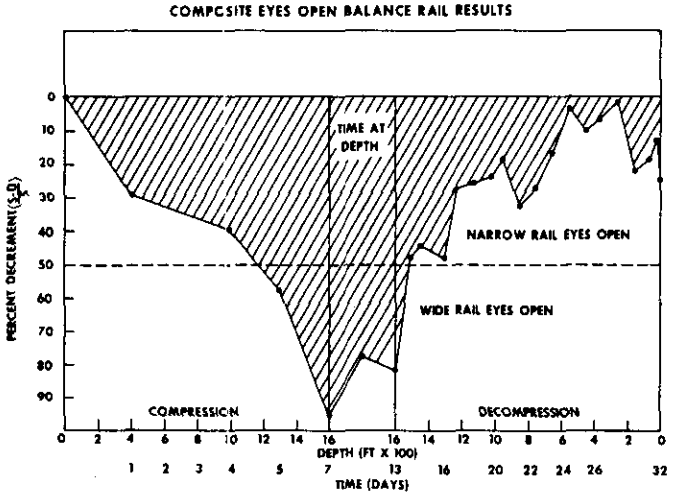

Fig. 9. Composite eyes open balance rail results.

published, we have somewhat arbitrarily joined these graphs on the common scale for demonstration purposes. This shows more clearly the continuous relationship to depth and the magnitude of the decrement below 1300 fsw.

Some adaption to the environment is shown by the improvement over time at 1600 fsw and by the statistically significant improvement in balance during decompression over that measured at comparable depths during compression. The results of this test do not indicate any particular mechanism for the disturbance.

Statometer. The results of the statometer test indicate the complexity of the postural equilibrium problem. Not only are there differences among individuals in their reponse to

pressure, but also the same individual's response will vary with depth and dive phase (compression-decompression). Attempts at utilizing accepted models of postural equilibrium to explain these results have met with only marginal success. Nashner (1970) has studied the various neural postural control systems and suggests that the following threshold and response times are appropriate for the listed control centers.

Control	*Threshold*	*Response time*
Muscle reflex	0	10 msec
Ankle deflection	.10° body angle	100 msec
Semicircular canals	.05°/sec	225 msec
Utricle otoliths	.29° body angle	225 msec
Vision	0	425 msec

To apply Nashner's findings to this study, one might think in terms of response time being related to frequency and threshold being related to amplitude. It is not quite this clear-cut, however, since a fast response with a high threshold can have the same frequency response as a slower response with a lower threshold. Observed amplitude and/or frequency changes, therefore, can be due to either changes in the neural response time, a shift in sensory threshold, or a combination of the two.

The two conditions (eyes open and closed) used during the statometer testing were intended to help isolate the location of any disruptive action. Parallel responses by the visual and labyrinthine postural control centers would tend to indicate that the site of the disruptive effect is not the vestibular system. A correlation of 0.92 indicates that there is a great deal of correspondence between the two test conditions. Although the postural equilibrium control with the eyes closed was not as precise as with eyes open, changes associated with increased pressure were very similar.

Perhaps one of the most intriguing findings in this study is the shift in the frequency response of the postural equilibrium control mechanism as the subjects passed through the 40 ATA-pressure level. This shift in frequency response was displayed for both the eyes-open and eyes-closed conditions for all six subjects. Similar transitory changes have been reported for intentional tremor and sleep EEG stages (Bachrach and Findling 1974; Wilcox and Russo 1974). Once through this disruptive pressure level, the subjects' response frequency returns to normal.

GENERAL

It is the opinion of the authors that the dysfunction of the postural equilibrium is another manifestation of the HPNS, the effect of the generalized *intention tremor* on the balancing mechanism. If this is true, measures of postural equilibrium provide reliable, reproducible means of quantifying this effect of the HPNS and may aid in its further investigation.

CONCLUSIONS

This study has demonstrated the existence of an impairment of postural equilibrium, which increased with pressure in a helium-oxygen atmosphere and which became especially severe and subjectively disturbing at about 31.3 ATA (below 1000 fsw). The results indicated that this impairment was not due to failure of either visual or vestibular inputs, but no further localization was possible. There is both subjective and objective adaptation to this

dysfunction with time at depth. In addition to the increases in amplitude of postural corrections with depth, there was a consistent, dramatic shift in the response frequency.

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Dr. Braithwaite is now with the Medical Information Science Department, University of California at San Francisco 94143. LCDR Berghage is now Deputy Chairman, Behavioral Sciences Department, Naval Medical Research Institute, Bethesda, Md. 20014.

Dr. Crothers' present address is 4115 E. Palo Verde Drive, Phoenix, Arizona 85018.

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Underwater Hearing Thresholds in Man as a Function of Water Depth*

JOHN F. BRANDT AND HARRY HOLLIEN

Communication Sciences Laboratory, Department of Speech, University of Florida, Gainesville, Florida 32601

Thresholds of human hearing were obtained underwater at depths of 35, 70, and 105 ft. Subjects were six divers experienced in taking underwater hearing-threshold tests by a modified Békésy technique. No significant effect resulting from the depth was noted. Threshold shifts (*re* air) for the three conditions of underwater hearing were consistent with those previously reported.

INTRODUCTION

Recently, Brandt and Hollien (1967) presented some data concerned with underwater hearing thresholds for pure tones. Part of those data included threshold sound-pressure levels (SPLs) from eight listeners at two water depths, 12 and 35 ft. While the difference was not statistically significant, the threshold SPL at 35 ft was greater than at 12 ft and increased with test frequency.

As part of a coordinated research program designed to define the parameters of underwater speech communication, further investigation of the effects of ear depth appeared warranted. As it seemed that increases in water depth—with concomitant increases in ambient pressure (water) upon the peripheral auditory system—might possibly be a limiting factor in underwater hearing, free-field audibility thresholds for pure tones were obtained at ear depths of 35, 70, and 105 ft by means of the fixed-frequency Békésy technique.

I. PROCEDURE

A. Test Facility and Apparatus

As the detailed procedure has been described previously (Brandt and Hollien, 1967; Hollien and Brandt, 1969), only a brief description is given here. The Bugg Springs field facility of the Naval Research Laboratory, Underwater Sound Reference Division, Orlando, Florida, was the site of the present research. Located directly over a deep fresh-water spring (temperature, 22°C) is a large floating barge, with two laboratory rooms situated one on either side of a well, through which the Diver Communication Research System, DICORS, (Hollien and Thompson, 1967) was lowered to the proper depth. DICORS is essentially an open-framework diving cage, constructed of polyvinyl chloride tubing, and is used to support subjects and equipment used in diver-communication research. It can be suspended in the water at any desired depth and is kept in place by guy wires.

The stimulus-generating equipment and response units also have been described (Brandt and Hollien, 1967; Hollien and Brandt, 1969). Sinusoidal test stimuli generated by a beat-frequency oscillator (General Radio, type 1304-B) were passed through an electronic switch (Grason-Stadler, model 829D) and associated equipment to a type J9 transducer mounted on the frame of DICORS, 1 m in front of the listener's ears. The J9 transducer was used as a sound projector (loudspeaker) for the audio range from 40 to 20 000 Hz. Calibration was accomplished by an F36 hydrophone, fixed to DICORS at the position of the diver's left ear. Acoustic signals emitted from the projector were transduced by the hydrophone and transmitted by cable to surface monitoring equipment.

Sinusoidal stimuli of 125, 250, 1000, 2000, and 8000 Hz were gated ON and OFF with a period of 500 msec, a 50% duty cycle, and a 2.5-msec rise-and-fall time. The attenuation rate of the recording attenuator was 8 dB/sec. Air-conduction thresholds were obtained by using a Rudmose (model ARJ-4) automatic audiometer,

* Presented at the 74th Meeting of the Acoustical Society of America, November, 1967 [J. Acoust. Soc. Amer. *42*, 1149(A) (1967)].

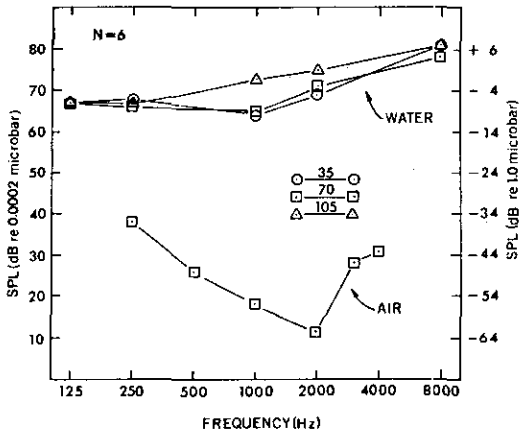

FIG. 1. Mean threshold SPL (decibels *re* 0.0002 μbar) as a function of test frequency in air and water at three depths. $N = 6$ diver/listeners.

modified to allow presentation of frequencies of 250, 500, 1000, 2000, 3000, and 4000 Hz.

B. Method

The research was carried out on six adult listeners (4 males and 2 females) who were competent divers with experience in taking hearing tests in air and water. When the diver was in position, had equalized the air pressure in the middle ear against the water pressure in the external auditory meatus, and was ready to begin the threshold test, he signaled the experimenter at the surface. The SPL of the test stimulus was first presented at a high enough SPL to be clearly audible. The diver/listener varied the SPL of the stimulus around the audibility-threshold level in the manner of the Békésy technique by activating a water- and pressure-proofed hand switch connected through a control box to the recording attenuator. As in earlier experiments (Brandt and Hollien, 1967; Hollien and Brandt, 1969), the threshold measures were taken while the listener was holding his breath. This procedure reduced the noise level of the medium to a minimum, since considerable noise is generated around the diver's ears when air bubbles are exhaled.

II. RESULTS AND DISCUSSION

The investigation was concerned with underwater hearing thresholds for pure tones at three ear depths, 35, 70, and 105 ft, and in air. Mean threshold SPLs for six divers as a function of frequency (Table I) are graphed in Fig. 1. The lower curve represents air-conduction thresholds and the three upper curves represent underwater thresholds. No statistically significant differences in threshold SPL due to ear depth were apparent. The increased thresholds at 1000 and 2000 Hz, at 105 ft, were probably the result of practice effects, as those conditions were the initial threshold conditions for all divers.

TABLE I. Mean threshold SPL (decibels *re* 0.0002 μbar) in air and water (three ear depths) as a function of frequency for six listeners. Standard deviations (decibels) are in parentheses.

Conditions	Frequency 125	250	1000	2000	8000
Water (35 ft)	66.8	68.5	64.3	68.8	81.2
	(5.6)	(5.7)	(7.9)	(6.6)	(14.0)
Water (70 ft)	66.7	66.2	65.3	71.3	78.2
	(5.8)	(6.6)	(7.2)	(9.5)	(14.6)
Water (105 ft)	68.2	67.0	72.8	74.8	80.8
	(9.2)	(8.4)	(12.6)	(13.7)	(14.4)
Mean Threshold	67.2	67.2	67.5	71.6	80.1
(taken over depth)	(7.3)	(7.1)	(10.3)	(10.6)	(14.4)
Air		37.5	17.8	11.2	
		(2.5)	(3.4)	(7.3)	
Difference (Water–Air)		29.7	49.7	60.4	

The underwater thresholds are from 30 to 60 dB higher than the air conductions, the difference increasing with test frequency. The underwater thresholds vary in frequency from 67 to 80 dB SPL, a range of about 13 dB, with a mean threshold of about 70 dB SPL. The threshold SPLs in air and water are in excellent agreement with our previously reported data (Brandt and Hollien, 1967; Hollien and Brandt, 1969).

The experiment can be summarized by reporting that increases in ear depth from 12 ft (previous experiment) to 105 ft (present experiment) and the concomitant positive increases in water pressure (5.3, 15.6, 31.2, and 46.7 psi at 12, 35, 70, and 105 ft, respectively) or corresponding increases in atmospheric pressure of 1.4, 2.1, 3.1, and 4.2 atm have no effect upon free-field underwater hearing thresholds in the frequency range between 125 and 8000 Hz.

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FISTULA OF THE ROUND WINDOW IN DIVING

CARL EDMONDS, MD

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OVER the last few years there has been valuable collaboration of diving medical specialists with otologists. Many otologic disorders are specifically associated with diving, and the development of standardized and refined otologic tests have allowed us to define the etiology and natural history of most of these causes of hearing loss and vertigo.[1] Diagnostic accuracy is necessary for the rational otologic management for two main reasons: the diversity of the otologic insult, and the tendency for most cases to heal spontaneously within a few weeks. The latter has resulted in a plethora of therapies which periodically emerge in the literature.

There remains a small but important group of divers who have sustained permanent damage to the inner ear. These cases are usually attributed to decompression sickness, as reviewed recently by Farmer,[2] or inner ear barotrauma, as validated by Freeman and Edmonds.[3]

This presentation deals with the latter disease and its relationship to labyrinthine window fistulae. We will first deal with background information and a definition of our terminology.

BACKGROUND

Normal nasal and eustachian tube function is a prerequisite for diving. Without it the subject is predisposed to develop middle ear barotrauma of descent. This is also known as ear squeeze, aerotitis media, aural or otitic barotrauma. It is caused by an inability to autoinflate the middle ear via the eustachian tube, when the diver descends. It is a frequent occupational disease of divers, and is the cause of many complaints of deafness. In some cases this is marked, but it is usually conductive in type and lasts only a few weeks. Rarely it is associated with inner ear damage, and this may be permanent. Cases have been presented[1,3] verifying that this hearing loss can vary from a partial to a total sensori-neural deafness, can be associated with any degree of vestibular hypofunction, and can occur concurrently with middle ear barotrauma or follow it by several days. The first four brief case reports illustrate these points. The disease entity is termed inner ear barotrauma.

CASE REPORTS

Case 1

An experienced diver with many normal audiograms had difficulty with autoinflation of his left ear during compression. He noted tinnitus following the dive and developed total nerve deafness over the next 24 hours.

Case 2

Another experienced diver with normal audiograms sustained a mild barotrauma of his left ear, associated with tinnitus. Twelve hours later he had an episode of vertigo and

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then progressively developed a total nerve deafness over the next few days.

Case 3

A physician had difficulty in autoinflation of his right middle ear during a dive to 7 meters. He complained of tinnitus and partial loss of hearing. This involved the high frequencies only, and has remained unchanged during the subsequent five years. There was no response from the affected ear to the conventional Hallpike caloric tests.

Case 4

This breathhold diver developed bilateral middle ear barotrauma. He also noted tinnitus and hearing loss. On examination he had the clinical otoscopic signs of middle ear barotrauma of descent, together with nystagmus and a bilateral partial sensori-neural hearing loss.

Case 5

This diver suffered bilateral middle ear barotrauma. He also noted tinnitus, then episodes of rotatory vertigo and finally a bilateral progressive sensori-neural deafness developing over the ensuing six days. Electronystagmography (ENG) demonstrated a mild spontaneous nystagmus. The more severely affected ear was explored and a rupture of the round window was found. Clear fluid was observed dripping out of the round window into the middle ear cavity each few seconds. The round window was plugged with a fat tissue graft and this prevented further leakage. Three days later a similar operative procedure was performed on the opposite side with a similar result. There was significant improvement in hearing on both sides, both subjectively and by audiometry. The ENG, to both positional and caloric testing, returned to normal.

Case 6

This diver noted a mild right middle ear barotrauma on descent, but then completed a dive in which he omitted correct decompression procedures. An hour later he developed marked prostrating vertigo and vomiting. Audiometry revealed normal hearing, and the ENG studies verified the brisk left beating nystagmus which could not be altered even with iced water caloric stimulation to the right ear. Left ear irrigation resulted in a temporary reversal to a right beating pattern. The patient was subjected to a prolonged oxygen recompression therapy with continuous ENG monitoring. No alteration was achieved in the degree of vertigo or nystagmus. Finally a tympanotomy was performed and a round window fistula was detected with fluid dripping freely into the middle ear cavity. This was repaired, with both subjective and ENG improvement. Positional nystagmus was markedly diminished, and when calorics could be performed there was a definite but impaired response to the Hallpike stimuli on the right side.

Case 7

This man had multiple system involvement as a result of decompression sickness. Recompression therapy required a rapid descent to 6 atmospheres absolute (ATA). As he was unconscious at the time, he was unable to autoinflate his middle ears, and he incurred the inevitable middle ear barotrauma. In the posttherapy period, he developed vertigo, nystagmus, and a right-sided hearing loss. A round window fistula was demonstrated on this side and was repaired. The slow seepage of bloodstained fluid from the round window contrasted with the greater flow of clear fluid in previous instances. The change in hearing was neither impressive nor rapid. There was the expected improvement in the conductive element of the hearing loss.

All the changes in the hearing of the first four divers were permanent.

Since 1970, and because of the seriousness of some of the cases, it has been our policy to surgically explore the middle ears of divers having severe or progressive sensori-neural deafness. This policy was adopted as a result of our observations on divers,[1,3] and our findings are in accord with the otologic literature on labyrinthine window fistulae. This has been described in the excellent presentations of Simmons,[4] Goodhill,[5] and Pullen.[6]

ROUND WINDOW FISTULAE

We have now observed round window fistulae in four instances, as a result of five surgical explorations. Without this investigation these instances would have

been classified as inner ear barotrauma, without further qualification. The pathologic findings would then have been presumed to be vasospasm, hemorrhage, or shock wave trauma to the sensory nerve endings depending on the bias of the clinician.

PATHOGENESIS OF ROUND WINDOW *FISTULAE IN DIVING*

As all the proved cases of round window fistulae in diving have been associated with middle ear barotrauma of descent, the simplest explanation is as follows: when the middle ear space contracts during the compression, or descent, the surrounding membranes which are amenable to distortion (the tympanic membrane and the round window) will stretch into the middle ear. Either may rupture, thus competing with mucosal hemorrhages and exudates as the pathologic mechanism of equalizing the middle ear pressure with that of the environment.

Other plausible and probably contributing etiologies have been proposed by Goodhill[5] and Freeman and Edmonds.[3] Both are related to the forceful Valsalva maneuvers that the diver performs in an attempt to overcome the discomfort of the middle ear barotrauma. The first involves a transmission of the associated increase in cerebrospinal fluid (CSF) pressure, through a patent cochlear aqueduct or internal auditory meatus, into the perilymphatic fluid and the labyrinthine window, exploding it into the middle ear. The second incriminates the successful performance of the Valsalva maneuver, with the excessive force being transmitted through the now patent eustachian tube to the middle ear and round window, imploding it into the perilymphatic system.

OBSERVATIONS AND RECOMMENDATIONS

Inner ear barotrauma is a permanent sensori-neural hearing loss or vestibular impairment, or both, in divers, as a complication of middle ear barotrauma. One verified pathologic result of inner ear barotrauma is a fistula of the round window.

Eleven incidents of round window fistulae in divers are known to these authors. Four have been reported by us, one by Pullen[6] and one by Schuknecht and Gacek.[7] Five others have not yet been reported. The reason for the apparent high incidence in divers is probably related to the effects of middle ear barotrauma and the Valsalva maneuver, as previously discussed.

In most of the cases the presentation is with sensori-neural deafness, which may be progressive and may follow the dive by hours or days. This presentation may reflect the understandable preoccupation, by both the diver and the medical attendant, with permanent cochlear damage — as opposed to the vestibular manifestations to which adaptation will occur. The initial vestibular symptoms may be of any intensity and may precede the hearing loss.

Hyperbaric oxygen therapy has been inadvertently or coincidentally administered in two of our cases of round window fistulae, and has had no noticeable influence on either vestibular or cochlear function. It is not meant to infer that this therapy may not be effective in other causes of inner ear disease associated with diving.

Operative exploration is thought to be indicated in those patients who have either severe or progressive sensori-neural deafness, and who do not respond to conservative management. Surgical

repair of the fistula has been performed in four instances by the authors. Substantial improvement in both cochlea and vestibular function has been demonstrated, but is not inevitable. The main purpose of this paper is to illustrate the existence of a labyrinthine membrane rupture as one pathologic basis for the clinical syndrome of inner ear barotrauma. It is not to promote the cause of surgery in the therapy of this lesion.

Care is required in both the conservative and the surgical management of these patients to ensure that the CSF and middle ear pressures are not raised. *Exercise, coughing, nose blowing,* straining at defecation, and performance of the Valsalva maneuver must be avoided. It is almost second nature for divers to attempt autoinflation of the middle ear if there is any abnormal otologic sensation. This autoinflation attempt, or the other causes of elevation of CSF pressure, could disrupt membrane repair whether occurring spontaneously or over a tissue graft.

Further exposure to diving, caisson work, or other hyperbaric environments must be prevented. Hypobaric conditions must also be considered hazardous, especially if the subject has a position of responsibility such as a pilot or navigator. Even commercial airplane flights as a passenger should be avoided until the fistula is presumed to have healed completely.

Key Words: Middle ear barotrauma; inner ear barotrauma; fistula of the round window; diving; sensori-neural deafness; case reports; vestibular impairment.

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DIVING INJURIES to the INNER EAR

JOSEPH C. FARMER, JR., MD

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DIVING INJURIES TO THE INNER EAR

JOSEPH C. FARMER, JR., MD

DURHAM, NORTH CAROLINA

SUMMARY — Most of the previous literature concerning otologic problems in compressed gas environments has emphasized middle ear barotrauma. With recent increases in commercial, military, and sport diving to deeper depths, inner ear disturbances during these exposures have been noted more frequently. Studies of inner ear physiology and pathology during diving indicate that the causes and treatment of these problems differ depending upon the phase and type of diving. Humans exposed to simulated depths of up to 305 meters without barotrauma or decompression sickness develop transient, conductive hearing losses with no audiometric evidence of cochlear dysfunction. Transient vertigo and nystagmus during diving have been noted with caloric stimulation, resulting from the unequal entry of cold water into the external auditory canals, and with asymmetric middle ear pressure equilibration during ascent and descent (alternobaric vertigo). Equilibrium disturbances noted with nitrogen narcosis, oxygen toxicity, hypercarbia, or hypoxia appear primarily related to the effects of these conditions upon the central nervous system and not to specific vestibular end-organ dysfunction. Compression of humans in helium-oxygen at depths greater than 152.4 meters results in transient symptoms of tremor, dizziness, and nausea plus decrements in postural equilibrium and psychomotor performance, the high pressure nervous syndrome. Vestibular function studies during these conditions indicate that these problems are due to central dysfunction and not to vestibular end-organ dysfunction. Persistent inner ear injuries have been noted during several phases of diving: 1) Such injuries during compression (inner ear barotrauma) have been related to round window ruptures occurring with straining, or a Valsalva's maneuver during inadequate middle ear pressure equilibration. Divers who develop cochlear and/or vestibular symptoms during shallow diving in which decompression sickness is unlikely, or during compression in deeper diving, should be placed on bed rest with head elevation and avoidance of maneuvers which result in increased cerebrospinal fluid and intralabyrinthine pressure. With no improvement in symptoms after 48 hours, exploratory tympanotomy and repair of a possible labyrinthine window fistula should be considered. Recompression therapy is contraindicated in these cases. 2) Vestibular end-organ injuries have been noted in three divers after sudden changes in inspired inert gases at a stable deep depth. They are postulated to result from transient intralabyrinthine osmotic pressure differences, or from bubble formations at labyrinthine tissue interfaces occurring with the counter-diffusion of the two dissolved inert gases at high partial pressures. Such injuries should be preventable by avoiding changes in inert gases at deep depths. 3) Inner ear injuries can be the major or only manifestation of decompression sickness. In a series of 23 such cases, a significant correlation exists between prompt recompression, relief of symptoms, and lack of residual deficits. The management of otologic decompression sickness is discussed. 4) Loud noise has been noted during helmet and chamber diving and has been associated with temporary threshold shifts in helmet divers. Appropriate damage risk criteria for noise exposure in compressed gas environments are needed, and potentially damaging noise exposures should be avoided.

Most of the previous literature concerning otologic dysfunction and injury related to diving and exposure to compressed gas environments has described barotitis media resulting from inadequate pressure equalization between the middle ear and the ambient atmosphere during descent or compression. This entity has been largely felt to be a reversible, middle ear problem and of relative minor importance to the health and safety of divers when compared to other diving injuries, such as air embolism and decompression sickness. Reports of inner ear disturbances related to diving have occurred relatively infrequently,

From the Division of Otolaryngology, Department of Surgery and the F. G. Hall Laboratory for Environmental Biomedical Research, Duke University Medical Center, Durham, North Carolina. This research was partially supported by the Office of Naval Research Contract N00014-75-C-0553 with funds provided by the Naval Medical Research and Development Command.

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are confusing, and/or are not well-documented. The purpose of this paper is to clarify the causes and treatment of inner ear injuries in diving in view of recent investigations and those performed under our direction.

Review of the previous literature reveals that Smith,[1] who first used the term "caisson disease," and other 19th century investigators,[2-6] described severe deafness and vestibular problems, among other systemic problems, in compressed air workers. Heller *et al*,[3] noted that permanent deafness in divers was not frequent and when seen, was secondary to interference with the cochlear blood supply by nitrogen bubbles which appeared in the labyrinthine vasculature during decompression. Alt *et al*[6] described bony and membranous semicircular canal and labyrinthine hemorrhages in animals subjected to rapid decompression. Lester and Gomez[7] used tuning forks and found decreased air and bone conduction in human subjects compressed in air at pressures of 3.0 and 3.5 atmospheres absolute (ATA).

Keays,[8] in a discussion of the epidemiology of decompression sickness, noted that 5% of such cases exhibited vertigo as a predominant symptom. He proposed that labyrinthine hemorrhage was the cause.

Boot[9] described "caisson workers' deafness," consisting of transient, conductive hearing losses secondary to Eustachian tube dysfunction aggravated by diving or permanent, neurosensory hearing losses related to excessive noise exposure, gas formation in the cochlea, labyrinthitis, or neuritis.

Vail[10] suggested that inner ear as well as middle ear trauma can occur in compressed air workers both during compression and decompression. Three rabbits and one dog were subjected to rapid compression and decompression. Histological examinations of the temporal bones of these animals by Dr. N. C. Foot showed hemorrhages in the middle ear cavity, mucosa, and submucosa with penetration of hemorrhage into the vestibule in one instance. No difference was noted between animals with and without Eustachian tubal occlusion. Conversely, "the structures of the internal ear, the mastoid cells, and the bone marrow of the temporal bone were little altered from their normal appearance; if there were lesions of these anatomic units, they were not evident." Vail summarized that ear damage during compression was related to inadequate middle ear pressure equalization which resulted in stasis and hemorrhage in the inner ear. Such injuries occurring during or shortly after the decompression were felt to be due to nitrogen bubbles causing emboli or necrosis in the inner ear.

Almour,[11] in a study of otologic problems of caisson workers, noted that symptoms of inner ear dysfunction may be transient or permanent. He stressed the importance of Eustachian tubal occlusion with subsequent otic barotrauma and tympanic membrane perforation during diving, and the need for predive audiometric surveys.

By 1940 decompression schedules for air diving had improved, and the apparent frequency of massive decompression sickness with inner ear injury decreased. A large increase in military diving occurred during World War II. From then until the late 1960s, investigators of otologic function in divers focused upon middle ear barotrauma, and descriptions of inner ear dysfunction in divers appeared rarely.

Shilling and Everley[12] noted high frequency sensorineural hearing losses in divers similar to damage from excessive noise exposure. They concluded that hearing losses in all diving groups were predominantly related to noise exposure or frequent barotitis media. Permanent deafness resulting from decompression sickness was felt to be rare. Behnke[13] stated that proven cases of permanent deafness related to diving injuries were rare and when seen, mostly consisted of high frequency hearing losses similar to a nondiving controlled group. Haines and Harris[14] pointed out the previous confusion in the literature as to the type of hearing losses experienced by divers. In a prospective study they noted only conductive and temporary hearing losses in association with barotitis media. Sen-

sorineural hearing losses in divers were felt to be mostly related to excessive noise trauma. This opinion was also reached by Taylor[15] in a study of 38 skin and scuba divers, and by Coles and Knight[16] in an analysis of the hearing acuity of British Royal Navy divers.

Kennedy[17] edited a detailed and comprehensive bibliography concerning vestibular problems in diving. In most of the literature cited, inner ear problems in diving were not well-documented and described symptoms suggestive of possible inner ear dysfunction or injury only as incidental observations. Such symptoms were often associated with more general, central nervous system (CNS) decompression sickness. When these symptoms were specifically described, adequate evaluations were frequently not done to precisely define the cause or extent of the injury.

During the past decade, more frequent human exposure to greater pressures and sea depths have occurred in both military and commercial diving as well as in sport diving. Recently, divers have worked on the ocean floor at depths as great as 305 meters and have reached simulated depths in laboratory chambers of 610 meters. With such exposures, Kennedy[18] has suggested that vestibular injuries are more common than previously suspected.

In recent years, reports of cochlear injuries with varying degrees of vestibular symptoms during diving have occurred with increasing frequency. MacFie,[19] Eichel and Landes,[20] Soss,[21] and Fields[22] have described inner ear injuries in scuba divers. Three of MacFie's four cases had associated middle ear barotrauma. He and Eichel and Landes postulated that these inner ear injuries during diving are related to increased gas pressures in the Eustachian tube and middle ear, with subsequent pressure distortion of the membranous labyrinth due to inward and outward displacement of the stapes footplate in the oval window. The resulting inner ear damage may be due to the shearing force of such movement or to hemorrhage from torn blood vessels. Simmons[23] reported on two cases of sudden deafness following diving. He postulated that these inner ear injuries resulted from a rupture, break, or dislocation of intracochlear membranes secondary to sudden increases in intracranial and intralabyrinthine pressures.

Stucker and Echols[24] suggested that inner ear injury during diving could be related to nitrogen bubble emboli in the internal auditory system occurring from too rapid decompression. In support of this suggestion, recent work by McCormick *et al*[25,26] has shown that guinea pigs subjected to rapid decompression developed intralabyrinthine bubble formations and hemorrhages plus decreases in the cochlear microphonic along with other manifestations of decompression sickness.

Other causes which have been suggested for inner ear dysfunction in diving include hypoxia, hypercarbia, nitrogen narcosis, alcoholic hangovers, sensory deprivation, hyperventilation, impure breathing gases, and unequal caloric stimulation.[27]

These possible etiologies encompass a wide variety of pathophysiological mechanisms, the management of which will be vastly different depending upon which mechanism is involved. The purpose of this paper is to present a new classification of inner ear dysfunction and injury occurring in diving, and to clarify the causes and treatment of these problems in accordance with recent investigations by us and others.

COCHLEAR FUNCTION DURING COMPRESSED GAS EXPOSURES WITHOUT APPARENT OTOLOGIC TRAUMA

Few studies of hearing during hyperbaric conditions have been done. As noted above, Lester and Gomez,[7] using tuning forks, found decreased air and bone conduction in human subjects at pressures of 3.0 and 3.5 ATA in compressed air. Bone conduction was decreased more than air conduction. Assuming that accurate hearing thresholds were found, the persistence of these changes for 24 to 48 hours after decompression suggests that the dives were not atraumatic and that otologic trauma, either barotrauma or decompression sick-

ness had occurred. Studies of hearing in compressed gas environments without apparent otologic trauma were reported by Fluur and Adolfson[28] who noted 30-40 dB middle frequency, conductive hearing losses in divers pressurized with air in a chamber to a simulated sea depth of 100.6 meters (11 ATA). Although the subjects had no subjective otologic complaints during the dive and received audiometric training before diving, the strong narcotic effect of nitrogen at these pressures raises the question of the feasibility of performing psychoacoustic studies during relatively deep air diving. However, the results obtained at pressure were reproducible and showed no significant alterations in bone conduction, while air conduction was significantly decreased in direct relationship to the increase in depth. Hearing returned to normal upon reaching surface. The authors postulated that the increased gas density at pressure resulted in an increase in middle ear impedance with decreased sound conduction to the inner ear.

Farmer *et al*[29] noted reversible and depth related, 20-30 dB, low frequency, conductive hearing losses in six asymptomatic divers pressurized in a chamber to 182.9 meters (19.2 ATA) with helium-oxygen. The concentration of nitrogen in these experiments was very low, and nitrogen narcosis was not a factor. Cochlear function as measured by the sensory acuity level technique and by studies of frequency difference limens was not altered at pressure. The low frequency conductive hearing losses, which disappeared gradually during decompression, were felt to be secondary to increased middle ear impedance from greater gas density at pressure, plus an increase in the middle ear resonance frequency resulting from the higher speed of sound in the helium atmosphere.

Later investigations by Thomas *et al*[30] of 33 divers during eight helium-oxygen chamber dives to simulated depths ranging from 91.44 to 305 meters, again showed reversible depth related, 20-25 dB conductive hearing losses in the lower frequencies. These losses occurred predominantly during the first 30.5 meters of compression with no further significant increases in thresholds at deeper depths. No alterations in cochlear function were seen. The divers experienced no otologic symptoms during any of these exposures. The changes observed were again felt to be related to increased impedance of the middle ear transformer in the dense gas with an upward shift of the middle ear resonance frequency in the helium atmosphere.

Psychoacoustic studies of hearing under hyperbaric conditions, particularly in helium atmospheres, must be interpreted with caution because of the large variability, ± 5 dB, between earphones as a function of pressure, within the same earphone during different pressurizations, and between compression and decompression.[31] Microphones, used for earphone calibrations, are relatively stable at pressure.[32]

Auditory thresholds measured in the water rather than in dry pressure chambers have been studied at various depths from 3.05 to 32 meters.[33-38] These investigations have shown threshold elevations ranging from 44 dB to 80 dB sound pressure level with no variation with changes in depth and no alterations of cochlear function. The results suggest that bone conduction is primarily responsible for hearing in wet, underwater conditions.

Changes in the auditory evoked responses (AER) as a function of depth and gas mixtures has been reported by several authors in laboratory animals and man.[39-43] Bennett and Glass[39] noted a reversible reduction of electroencephalographic spontaneous activity as well as the auditory evoked potential in cats at increased pressures of nitrogen and argon. Further work by Bennett *et al*[44] in humans has shown that the AER decreases to a lesser degree in compressed helium-oxygen atmospheres than in compressed air and helium-nitrogen-oxygen atmospheres. Also, decreases in the AER have been noted in humans while breathing oxygen at 1, 2, and 3 ATA. These findings have been related to oxygen toxicity, nitrogen narcosis, and hydrostatic pressure effects upon the CNS

with subsequent changes in the synaptic and dendritic areas of the brain and alterations in nerve conduction. Indeed, by other methods, similar changes have been noted by measurements of visual evoked responses.[44] However, the amplitude of the AER is directly related to the intensity of the auditory input signal. Thus, the above noted conductive hearing losses[28-30] and the decreased output of auditory transducers[31] in hyperbaric atmospheres could explain the observed decreases in the AER since the amplitude of the input signal was not corrected for depth in any of these studies. The greater AER depression observed in compressed nitrogen atmospheres was possibly due to the greater conductive hearing losses in these gases than in compressed helium.

While alterations in human CNS function apparently occur with exposure to increased pressures of nitrogen, helium, and oxygen, no definite changes in cochlear function have been demonstrated during such exposures. Only depth related conductive hearing losses have been noted during air diving to depths of 100.6 meters and helium-oxygen compressions to depths of 305 meters. As men are exposed to greater depths, future studies will be needed to determine whether cochlear function is altered during deep dives in the absence of barotrauma or decompression sickness.

Investigations of cochlear potentials in laboratory animals during compressed gas exposures designed to avoid barotrauma and decompression sickness have shown mixed results. Miller[45] reported losses in cochlear potentials in cats during pressurizations to 11 ATA in air and in helium-oxygen. These losses recovered infrequently with decompression. Preliminary, unpublished observations in our laboratory have shown mixed results in measurements of cochlear microphonic and VIII nerve action potentials in guinea pigs during air dives designed to avoid barotrauma and decompression sickness. With middle ear structures removed, cochlear microphonic and VIII nerve action potentials from air conducted stimuli showed a progressive decrease to 3 ATA with recovery upon return to surface. During bone conducted stimulations, these parameters showed no changes as a function of pressure. With intact middle ears, but with open bullae, the cochlear microphonic and nerve action potentials showed a progressive loss to 3 ATA. During return to surface, additional losses in cochlear microphonics occurred, and the VIII nerve action potentials showed only partial recovery. These changes are possibly related to cochlear damage from excessive chamber noise during the experiments. Noise levels as high as 120 dBA were noted during compression. With the middle ears intact, inner ears were more exposed to this noise. Thus, the results cannot be attributed to the effects of compressed air alone upon cochlear function. Further studies are continuing in order to understand these findings.

TRANSIENT VESTIBULAR DYSFUNCTION DURING DIVING

In terrestrial environments, the perception of position and motion is dependent upon CNS integration of information from the visual, proprioceptive, and vestibular systems. During underwater conditions, visual and proprioceptive inputs frequently become distorted. Thus, proper spatial orientation under such conditions becomes more dependent upon information received from the vestibular system. In most diving situations, the vestibular end-organs are stimulated equally, the central vestibular structures function normally, and vertigo does not occur. However, in certain types of diving, transient vertigo and nystagmus have been noted. Such occurrences with possible nausea and vomiting can present significant and potentially life-threatening dangers to divers.

Transient vertigo and dizziness have been described with breathing high partial pressures of nitrogen, oxygen, and carbon dioxide, and during hypoxia. However, these symptoms are probably related to the effects of these conditions upon the CNS and not to primary vestibular system dysfunction.[27] Multiple electronystagmographic (ENG) studies in our laboratory have shown no true

nystagmus in divers at depth during nitrogen narcosis or with increased partial pressures of arterial oxygen, but without obvious signs of CNS oxygen toxicity.

Transient Vertigo due to Caloric Stimulation during Wet Diving. In certain diving situations, unequal vestibular end-organ stimulation with subsequent vertigo and nystagmus occurs especially when there is preexisting ear disease. Unequal entry of cold water into the external ear canals secondary to obstruction of one canal by cerumen, otitis media, ear plugs, or bony exostoses can produce a caloric response, particularly when the diver is oriented in a position in which the lateral semicircular canal is in a vertical plane.[27,46] Tympanic membrane perforations resulting from middle ear barotrauma during descent or preexisting middle ear disease can result in transient vertigo from the unequal stimulation of one semicircular canal by the entry of cold water into the middle ear.[24,27]

Transient Vertigo Resulting from Unequal Middle Ear Pressure Equilibration during Diving (Alternobaric Vertigo). Transient vestibular dysfunction related to unequal middle ear pressure equilibration has been described during ascent by Lundgren,[47] who coined the term "alternobaric vertigo," Vorosmarti and Bradley,[48] Terry and Dennison,[49] and, during descent, by Edmonds *et al.*[27] Lundgren attributed this phenomenon to increased middle ear pressure in one ear during ascent with resulting unequal vestibular end-organ stimulation. He noted that some individuals who experienced alternobaric vertigo at depth could produce vertigo and vestibular nystagmus by performing the Valsalva's maneuver, and unequally inflating the middle ears at surface. Many of these divers had noted asymmetrical ear clearing during ascent while diving. The subsequent vertigo disappeared with stopping the ascent, descending again, or shortly after a sudden hissing of air into the blocked ear. Tjernström,[50] using a unique, nontraumatic technique for observing middle ear pressure changes with simultaneous ENG recordings, has shown true vestibular nystagmus with asymmetrical equilibration of middle ear pressures during ascent in shallow chamber dives.

The exact frequency of alternobaric vertigo in diving is not known. Lundgren *et al,*[51] in a more recent work involving a questionnaire answered by 2,053 Swedish divers, indicates that of 453 divers who had experienced vertigo during diving, 343 or 16.7% of all divers surveyed were likely to have had alternobaric vertigo. Ninety-seven percent of these divers indicated that the vertigo lasted from a few seconds up to ten minutes. Also, divers who had experienced vertigo had logged more dives than divers without vertigo experience, and had reported more frequent instances of ear-clearing problems during diving. These middle ear pressure equilibration difficulties were usually more dominant in one ear. Thus far, only one instance of persistent inner ear injury resulting from apparent alternobaric vertigo during ascent from which decompression sickness was unlikely has been reported.[27]

The best treatment of alternobaric vertigo is that of prevention. Individuals should not dive if difficulty with ear clearing exists or if a Valsalva's maneuver at surface produces vertigo. If a diver notices any ear fullness or vertigo during compression, further descent should be stopped and the diver should ascend until the ears can be cleared. If such symptoms are noted during ascent, the ascent should be abruptly stopped, and the diver should descend until his symptoms disappear, if gas supplies and other conditions permit. Also, diving with a companion is always a safe precaution.

Transient Disequilibrium Associated with Deep Helium-Oxygen Diving. Brauer,[52] Buhlmann *et al,*[53] and Bennett and Towse,[54] during experiments attempting to extend human depth capabilities, described a syndrome of vertigo, generalized intention tremor, and decrements in psychomotor performance in divers who underwent rapid compression with helium-oxygen mixtures at deep depths, usually greater than 152.4

meters. These symptoms and abnormalities were relieved within a few hours after compression ended, and were not related to excess partial pressures of oxygen or carbon dioxide, nor to hypoxia. The severity of the symptoms increased with faster compression rates at deeper depths. This syndrome was called the "high pressure syndrome," (HPNS).

In one of these experiments,[53] one subject developed a significant neurosensory hearing loss during decompression. This occurred several days after leaving the bottom depth and after the symptoms noted during compression had subsided. Otherwise, no other otologic symptoms were noted in any of the subjects during or after these dives.

In a series of experimental dives during 1973, Bennett *et al*[55] noted that the symptoms of the HPNS could be significantly reduced by adding nitrogen to the helium-oxygen mixtures used in such dives. Divers were rapidly compressed to 219.5 meters with 25% nitrogen in helium-oxygen and to 305 meters with 18% nitrogen in helium-oxygen. Hypoxia was not a factor because oxygen tensions were maintained at 360 mm Hg. Measurements of EEG and tremor plus psychomotor and intellectual performance were compared with similar studies done during helium-oxygen dives without nitrogen to the same depths using similar compression rates. During the dives using nitrogen, tremors were completely suppressed and psychomotor performance improved, with nausea and dizziness disappearing. Some decrement in intellectual performance persisted. This was attributed to mild nitrogen narcosis.

In the same series of dives, Farmer *et al*[56] performed ENG recordings on each subject, and noted no definite vestibular nystagmus during any of the compressions with helium-oxygen alone in which the classical symptoms of the HPNS were present. Ocular tremor was present on the recordings and was decreased in those dives with nitrogen. Also, no nystagmus was noted in the trimix (helium, oxygen, and nitrogen) dives even though evidence of mild nitrogen narcosis was present. The dizziness experienced with the HPNS was described by the subjects as an unsteadiness without sustained vertigo, but with excessive movement of the field of vision upon head turning. No other otologic symptoms were noted during or after any dive. The results suggest that the symptoms of dizziness and nausea described with the HPNS are not secondary to unilateral dysfunction of the vestibular end-organs and/or primary vestibular neurons.

Braithwaite *et al*[57] performed ENG with mental alerting, pendulum tracking, optokinetic stimulation, cold caloric stimulation and positional testing, along with balance rail tests and statometer (standing steadiness) tests on six divers during a 487.7 meter (49.48 ATA) helium-oxygen chamber dive. Symptoms of HPNS were present. Similar results to those seen in our experiments were noted with all measures of vestibular function remaining unchanged from previous surface data. However, performance on the balance rail and statometer deteriorated in association with increased depth, especially greater than 396.2 meters. Some adaptation with time occurred. These investigators concluded that the dysfunction of postural equilibrium observed represented another manifestation of the HPNS, and was related to the effect of the generalized intention tremor upon the balancing mechanism. Similar results have been described by Adolfson *et al*, who noted no changes in the vestibulo-ocular reflex with increasing depth during atraumatic diving,[58] and also observed that body sway did increase as pressure increased.[59]

We postulate that the increase in body sway plus the subjective dizziness and nausea of the HPNS could be related to a decrease in the normal cerebellar inhibitory modulation of the vestibular nuclei. This decreased cerebellar inhibitory activity is possibly similar to the previously observed decrease in EEG measured cortical activities seen with visual evoked responses during deep helium-oxygen diving.[44] Both the right and left vestibular nuclei would be affected equally, resulting in an

equal increase in impulse frequencies over the right and left central vestibular connections: *i.e.*, the vestibuloocular tracts, the vestibulospinal tracks, and the vestibulovagal connections with resulting ocular and limb tremor plus nausea. Because of the equal changes in both vestibular nuclei, sustained, rotary vertigo and nystagmus are not noted. Further electrophysiologic studies of the vestibular system in animals during deep helium diving with rapid compression are continuing in order to evaluate this hypothesis and better understand the apparent dysfunction of the central vestibular system during these conditions.

PERSISTENT INNER EAR INJURY IN DIVING

Analysis of recent reports plus our own investigations of persistent cochlear and vestibular injuries in diving indicate that the mechanisms of such injuries and proper treatment thereof differ, depending upon in which type of diving the injury occurred. Therefore, these injuries should be organized as occurring: 1) during descent or ascent in relatively shallow diving with little likelihood of decompression sickness or during compression in deeper diving, 2) at stable deep depths, 3) during or shortly after ascent or decompression from dives in which decompression sickness is possible; and 4) those related to high background noise during diving conditions.

Injuries Occurring during Descent or Ascent in Relatively Shallow Diving or during Compression in Deeper Diving (Inner Ear Barotrauma). Much of the diving community has discounted the possibility of significant inner ear injury occurring in association with middle ear barotrauma encountered during descent or compression. However, analysis of recently reported cases of diving-related cochlear damage[19-23] indicates that these injuries occurred during relatively shallow air diving in which decompression sickness is unlikely.[60] Many of the cases were associated with the symptoms or physical findings of middle ear barotrauma during compression.

Freeman and Edmonds[61] described five experienced divers who developed significant neurosensory hearing losses with and without vertigo during or shortly after shallow air dives in which decompression sickness was an unlikely contribution factor. Each diver had difficulty with ear clearing during descent or exhibited evidence on otoscopic examination of middle ear barotrauma. Each case was well-documented with timely pre- and postdive audiograms. The neurosensory losses observed were of varying degrees and patterns and did not recover with subsequent examinations. The authors postulated that the sudden outward movement of the stapes which could occur with sudden clearing of the middle ear by a forceful Valsalva's maneuver could result in cochlear damage.

Goodhill[62] reviewed reports of oval window fistulae[63,64] and described fistulae of the round and/or oval windows in three patients who suffered sudden, stress related neurosensory hearing losses. He proposed that with a forceful Valsalva's maneuver or straining, intracochlear pressure rises by transmission of the accompanying increased CSF pressure through a patent cochlear aqueduct. The resulting pressure differential between the perilymphatic space and the middle ear causes a rupture of the round window membrane and/or oval window ligament with leakage of perilymph into the middle ear. Goodhill also proposed that during a forceful Valsalva's, a sudden rise in middle ear pressure could cause an "implosive" force upon the round window membrane or oval window ligament with possible rupture of these structures and/or, as Simmons[23] proposed, ruptures of intralabyrinthine structures, such as Reissner's membrane, basilar membrane, saccule, utricle, or semicircular canals.

In an editorial comment, Goodhill[65] suggested that round window membrane and/or oval window annular ligament ruptures with resulting perilymph leaks could explain the inner ear injuries in the five diving cases reported by Freeman and Edmonds.[61] He stressed that potentially reversible cochlear injuries could occur in divers without decompression sickness, and suggested that exploratory tympanostomies

be performed in such patients if improvement in inner ear dysfunction did not occur after 48 hours of bed rest.

Pullen[66] reported a round window rupture in a 40-year-old male who developed a sudden neurosensory hearing loss in the left ear three days after an asymptomatic 9.14 meter scuba dive. Decompression sickness was unlikely after such an exposure. Surgical repair of the fistula resulted in a return of the hearing to normal. Pullen also noted that the round window membrane in this case, as well as in two other patients with round window fistulae not related to diving, was quite visible and angled less than usual.

Schuknecht and Gacek[67] described a round window rupture in a 21-year-old male who had suffered vertigo, nausea, and vomiting with a left-sided hearing loss shortly after a 3.66 meter scuba dive during which he had sharp pain and a plugged sensation in his left ear. Again, decompression sickness was unlikely after this dive. The vertigo subsided during the subsequent two days, but the hearing loss persisted. Immediate surgery was performed when the patient presented with a severe neurosensory loss one week after the dive. After repair of a marginal, linear tear in the round window membrane, subsequent examination showed progressive improvement in hearing with a persistent loss in the high frequencies.

Edmonds *et al*[68] have more recently observed four instances of round window fistulae in three divers, each of whom suffered middle ear barotrauma plus neurosensory hearing loss and/or vertigo during diving. Five other cases were mentioned but not described. One of the divers had bilateral involvement after a dive in which decompression sickness was unlikely. The most severely affected ear was explored first, and the second ear was operated upon three days later. Round window ruptures were repaired in each ear, and significant hearing improvements subsequently occurred. The second diver suffered severe vertigo and vomiting one hour after a dive during which he experienced mild right ear pain and fullness on descent, but completed the dive, and omitted proper decompression stops during ascent. Postdive, he had a left beating nystagmus and a normal audiogram. No improvement occurred with oxygen recompression treatment. During subsequent right exploratory tympanotomy, a round window rupture was repaired. Postoperatively, he recovered. The third diver developed bilateral middle ear barotrauma when he was recompressed rapidly for treatment of CNS decompression sickness. Because he was unconscious, he was unable to clear his ears during recompression. Shortly after treatment, he developed vertigo and right nerve deafness. At surgery a right round window fistula was repaired and minimal improvement in hearing occurred postoperatively. Otologic decompression sickness in addition to round window rupture was a possible contributing factor in this case and in the second case. The authors note that cases of round window fistulae in divers in most instances present with neurosensory deafness which may be total or partial, occur with varying degrees of vestibular dysfunction, can be noted concurrently with middle ear barotrauma, or can follow the diving exposure by hours or days, at which time the signs of middle ear barotrauma may have subsided.

Although no definite case of rupture of the oval window annular ligament in divers has yet been reported, Goodhill *et al*,[69] in a description of 15 cases of labyrinthine window fistulae associated with sudden deafness, found that oval window perilymph leaks were more common. In ten cases the injuries were in the oval window annular ligament area; four cases involved both windows; one case involved only the round window. Surgical repair of these injuries resulted in varying degrees of improvement in most cases. No specific mention of diving was made in any of the 11 cases who had a history of physical stress prior to the onset of the sudden deafness. In one case, an oval window annular ligament tear was found in a 52-year-old male who had noted a sudden hearing loss and tinnitus while

swimming, but with no mention of diving.

In a recent animal study Harker *et al*[70] found that increases in CSF pressures resulted in bulging and/or rupture of the round window membrane in 15 out of 18 cat preparations. Eight membranes exhibited only bulging with seven showing rupture and accumulation of fluid in the round window niche. The lowest increase in CSF pressure which resulted in round window bulging was 80 mm Hg. The lowest pressure which caused rupture was 120 mm Hg. In the same studies, using India ink dye, the cochlear aqueduct was noted to be the predominant channel of communication between the subarachnoid and perilymphatic space. Dye was concentrated along the internal auditory nerve and reached the modiolus, but did not penetrate further along the nerve channels to the habenula perforata.

Thus, animal studies and reports of human injuries definitely indicate that inner ear injury can occur during shallow diving, and that such injuries can involve round window ruptures and labyrinthine fistulae. The exact frequency of these injuries and of associated round window ruptures are not known. From the work of Goodhill *et al*,[69] tears in the oval window ligament during diving are possible. Injuries to intralabyrinthine structures, such as Reissner's membrane, as postulated by Simmons,[23] with and without associated labyrinthine window disruption are also possible. However, round window rupture is the only abnormality thus far demonstrated in association with persistent inner ear dysfunction occurring with shallow diving.

The likely mechanism of these injuries in diving is depicted in Figure 1. With adequate middle ear clearing during descent, intracochlear pressure as well as ambient pressure increases relative to middle ear pressure. With straining or a Valsalva's maneuver, a further increase in the pressure differential between the middle ear and inner ear will occur from the transmission of the accompanying increased CSF pressure to the perilymphatic space through the cochlear aqueduct, as proposed by Goodhill.[62] When a critical pressure differential is reached, the round window ruptures into the middle ear.

With continued descent and a non-cleared ear, the pressure differentials between the inner and middle ear could reach a critical level and round window ruptures could occur without an accompanying Valsalva's maneuver. If the data from the studies in cats by Harker *et al*[70] can be applied to humans, round window rupture could theoretically occur with a pressure differential of 120 mm Hg between the inner and middle ear. Such a pressure differential is equivalent to a depth difference of approximately 1.58 meters of sea water.

Some of the inner ear injuries noted with shallow diving could represent a more severe form of "alternobaric vertigo" as described by Lundgren[47] and suggested as a cause of injury in one case by Edmonds *et al.*[27] With inadequate middle ear clearing during ascent, middle ear pressure will rise relative to intralabyrinthine pressure. When a critical pressure difference is reached, the round window could rupture, allowing gas bubbles to leak into the perilymphatic space with perilymph being displaced into the middle ear.

With rapid or sudden emergency ascents from depth, divers can develop intra-arterial air emboli from rupture of lung alveolar membranes by rapidly expanding gases.[60] These emboli could theoretically travel to the labyrinthine arterial system and cause ischemia and infarction of the membranous labyrinth. However, no case of documented inner ear injury in association with the pulmonary, cardiovascular or CNS signs of air embolization during diving has been described. Also, such otologic injuries are unlikely in the absence of these more life threatening findings.

The best treatment of inner ear injuries during shallow diving is prevention. Individuals who have difficulty with ear clearing should not dive until such difficulty subsides. Whenever otologic symptoms are encountered during descent or compression, the dive should be halted, with the diver ascending un-

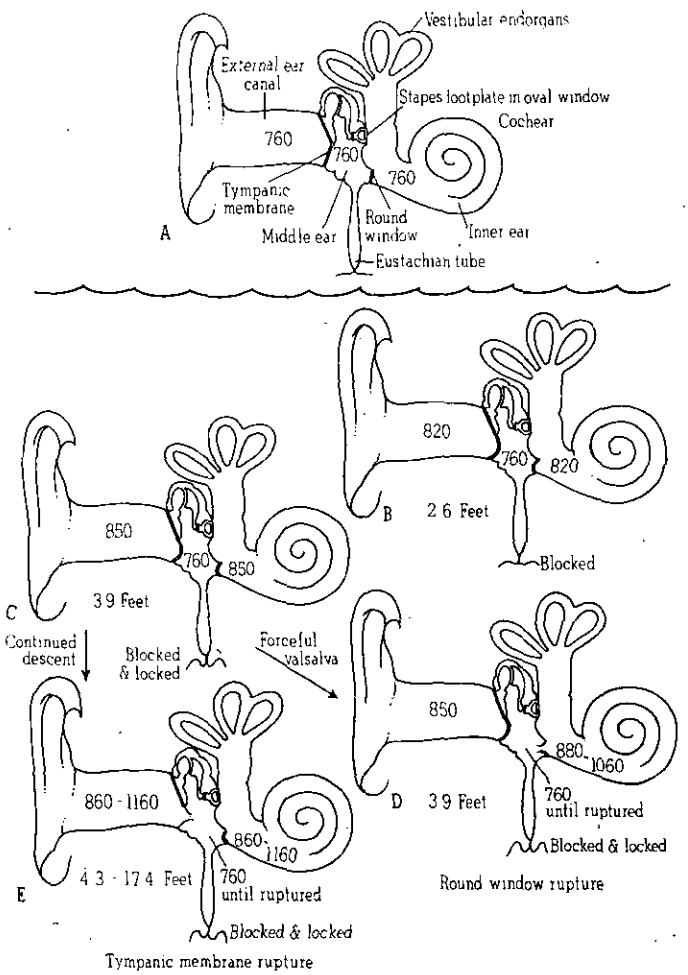

Fig. 1. Otologic barotrauma during descent. Theoretical sequence of events in the right ear of a diver who does not equilibrate middle ear pressure during descent. Pressures are shown in mm of mercury (Hg). A) Surface condition with equal pressures (760 mm Hg) throughout and patent Eustachian tube with normally closed nasopharyngeal ostium. B) Depth of approximately 2.6 feet (0.79 meters) after diver failed to open the Eustachian tube upon entering the water. Pressure differential of 60 mm Hg exists. Tympanic membrane and round window are bulging into the middle ear. Diver notices pain and pressure[89] in the ear with a conductive hearing loss and possible vertigo. C) Depth of approximately 3.9 feet (1.19 meters) with 90 mm Hg pressure differential and blocked and locked Eustachian tube.[89] D) Forceful Valsalva's maneuver can lead to rupture of the round window with resulting leak of perilymph into the middle ear.[93] The exact pressure differential at which rupture occurs in humans is unknown. Studies in cats[70] have indicated that round window ruptures occur when a pressure of 120-300 mm Hg is applied to the CSF space at 1 ATA. E) Continued descent can lead to tympanic membrane rupture at pressure differentials of 100-499 mm Hg or depths of 4.3-17.4 feet (1.31-53.04 meters). Actual rupture point is quite variable.[89] (Illustration and legend modified from Figure 9-2, Strauss RH (ed); *Diving Medicine*. New York, Grune & Stratton, 1976, p 118.)

til the ear clears, even if he has to return to the surface.

Any diver who experiences persistent vertigo, neurosensory hearing loss, or tinnitus following dives in which decompression sickness is unlikely, should be considered as a possible case of inner ear barotrauma and perilymph fistula. Such divers should be immediately placed on bed rest with head elevation. Care should be taken that CSF and middle ear pressures are not increased through the avoidance of exercise, coughing, nose blowing, straining with defecation, and the performance of the Valsalva's maneuver.[68] If no improvement in the hearing loss and/or vestibular signs occurs within 48 hours, an exploratory tympanostomy for closure of a possible perilymph fistula should be considered.[65]

Pang[71] reports two cases of inner ear injury following diving which improved with hyperbaric oxygen therapy. One case involved a short dive only to a depth of 2.44 to 2.74 meters. Decompression sickness from such an exposure is highly unlikely.[60] The other case consisted of three repetitive dives to depths of 36.6 meters in which decompression sickness was possible. While the exact mechanism of inner ear injury in these two cases was undetermined, it is unlikely that the diver involved in shallow exposure suffered from decompression sickness or air embolism, and that hyperbaric oxygen therapy had a beneficial result. If a labyrinthine window rupture existed, recompression exposed the diver to the same pressure changes which initially caused the injury. Fortunately, in this case, recovery occurred in spite of this therapy. Divers who suffer inner ear symptoms following dives in which decompression sickness is unlikely and who do not exhibit signs of systemic air emboli, should not be treated with hyperbaric oxygen therapy because recompression with a labyrinthine window fistula might result in further inner ear injury. In cases where decompression sickness is likely or in cases with more serious signs suggestive of air embolism, recompression therapy should be promptly administered; however, with no improvement in the inner ear function, a labyrinthine fistula should be considered as a cause of the injury.

Otologic Problems Occurring at Stable Deep Depths. Inner ear problems occurring while at stable deep depths have been described by Sundmaker[72] and Lambertsen.[73] These investigators noted three divers, each of whom during a deep, experimental, chamber dive at the University of Pennsylvania during late December 1971, sustained a unilateral loss of labyrinthine function which began while at stable deep depths, ranging from 183 to 335.3 meters. The sudden onset of vertigo, nausea, and nystagmus occurred shortly after the subjects began breathing by mask a gas mixture which contained a second inert gas, nitrogen or neon, in addition to the background helium-oxygen atmosphere. These experiments were undertaken to investigate the effects of these gas mixtures upon diver performance. As a result of the changes in inspired gases, the partial pressure of helium was thus decreased and replaced by a second inert gas while the total pressure remained the same. Oxygen partial pressure was unchanged and remained at a safe level. Preceding this event, no otologic symptoms had been noted during the dive. Each subject, shortly after the gas change, noted the sudden onset of vertigo and nausea, and was observed to have nystagmus. No changes in auditory function occurred and no evidence of CNS dysfunction was found. Extensive follow-up evaluation after the dive revealed a total unilateral loss of labyrinthine function in one subject, a partial unilateral loss in another subject, and a recovery of function after an initial partial unilateral loss in the third subject. Audiometric studies showed no changes in hearing.

We propose two theories as to the etiologies of these injuries. Both theories take into account the sudden onset of symptoms shortly after the initiation of breathing a mixture in which helium was partially replaced by another inert gas. The first theory suggests that with the sudden addition of a second inert gas at

deep depths, the rate of increase in the concentration of this dissolved gas in the perilymph and endolymph is significantly different because of the differences in blood supply to these two areas, as previously demonstrated by Axelsson.[74] Thus, one extrapolates that the concentration of dissolved inert gas rises at a faster rate in endolymph than in perilymph, and a transient, but significant difference in osmotic pressure develops between these two spaces. This results in a flux of water into the endolymphatic space with endolymphatic hydrops and possible rupture of Reissner's membrane. The second theory involves the counter diffusion of dissolved inert gas molecules between inner ear compartments. When divers change from one breathing mixture to another at stable deep depths, the diffusion of the newly dissolved inert gas into body tissue and fluid spaces with the reversed diffusion of the previous dissolved inert gas can result in bubbles at tissue interfaces, such as the partitions in the inner ear between the perilymphatic and endolymphatic spaces. This bubble formation occurs without changes in total ambient pressure and produces displacement and/or disruption of inner ear structures. Blenkarn *et al*[75] and Graves *et al*[76] have noted gas filled blister formations in skin following the sequential exposure of various inert gases at constant ambient pressures. This eruption is felt to represent gas bubble formations in the deeper layers of the skin, resulting from the counter diffusion of the different inert gases across tissue interfaces.

The understanding of the mechanisms of inner ear injuries occurring at stable deep depths in association with changes in inert gas composition requires further investigation. If either of the two above theories is correct, such injuries should be alleviated by avoiding changes between inert gases at deep depths.

Persistent Inner Ear Injuries Occurring during or shortly after Ascent or Decompression (Otologic Decompression Sickness). Most of the previous literature concerning decompression sickness has mentioned otologic manifestations in association with skeletal, joint, or CNS bends, where inner ear symptoms were of secondary importance and possibly related to centrally located lesions.[1-5,18,77] Inner ear dysfunction has been felt to be rare with decompression sickness.[8,12,14] Frequently, hearing loss, and to a lesser extent, vertigo in divers have been ignored.[18]

With more frequent exposures to deeper depths in recent years, reports of vertigo and/or hearing loss during or following decompression have occurred. Buhlmann and Waldvogel[78] in a report of 82 decompression accidents during a series of dives ranging in depths from 100.6 to 221.3 meters (11 ATA to 23 ATA) noted that the only neurological symptoms in the entire series consisted of vertigo, nausea, vomiting, and tinnitus in 11 cases, with hearing loss being noted in two of these. These symptoms appeared only during decompressions from the deepest dives, depths of 147.8 and 221.3 meters. Nine of the 11 cases required recompression treatments, whereas, a smaller portion (49 out of 71) of the remaining, noninner ear accidents required treatment.

Gehring and Buhlmann[79] more recently described 12 cases of inner ear symptoms consisting of vertigo, nausea, and vomiting after 24 decompressions from depths ranging from 42.05 to 305 meters (5.2 ATA to 31 ATA). In four cases there were associated hearing losses and tinnitus. With dives using longer decompression schedules, these investigators did not note ear symptoms.

We have studied 23 cases of vestibular and/or cochlear injuries occurring during or shortly after decompression.[80] These cases were selected from reports of military and civilian diving accidents on file at the US Naval Experimental Unit and from cases referred to us. One case occurred at our institution. Ten of these cases had been previously described by Rubenstein and Summitt.[81] No cases were included in which the divers: 1) had difficulty clearing their ears during compression, 2) described ear symptoms while at the maximum depth, or 3) were exposed to uncon-

trolled or rapid, emergency ascents with possible air emboli. Also, cases with insufficient information or with signs of hypoxia, hypercarbia, or other neurological symptoms suggestive of CNS decompression sickness were excluded.

In this series, the 11 divers who were recompressed within 42 minutes after the onset of otologic symptoms during or after ascent experienced relief during recompression and had no residual inner ear dysfunction. Of the three divers treated within 60 to 68 minutes after symptom onset, one diver experienced relief of symptoms. The other two had only partial or no relief, and exhibited significant residual hearing loss or vestibular dysfunction. Cases in which recompression treatment was not administered or was delayed longer than 68 minutes after symptom onset exhibited either prolonged relief or no relief with residual inner ear dysfunction.

Thus, a significant correlation between prompt recompression treatment and recovery is apparent. This, plus the fact that the symptoms all began either during or shortly after decompression, strongly suggests that these symptoms are a form of decompression sickness and are related to bubble formation either in the perilymph or endolymph spaces, or in the internal auditory artery system. Otic barotrauma is an unlikely contributing factor in this series, in that no diver noted difficulties with ear clearing during compression. Other possible mechanisms of injury include hemorrhage into the inner ear, disruption of labyrinthine structures, vascular spasm, or thrombosis with subsequent labyrinthine ischemia. However, with these problems, one would not expect to see relief with prompt recompression.

Twelve of the 19 helium exposures involved dives in which the otologic symptoms began with or after a switch to an air atmosphere at depths ranging from 18.29 to 45.72 meters during the latter stages of decompression. In one additional case the symptoms began before, but became more severe during the air switch. Such a practice is common during decompression from deep helium oxygen dives, and is felt to accelerate the removal of helium from tissues with shortening of decompression time. This sudden change in gas composition possibly contributes to the tendency for dissolved helium molecules to go into the gas phase with bubble formation in tissues during decompression. It is also possible that the counter diffusion of the two different inert gases between inner ear fluid compartments results in bubbling at compartmental interfaces in a manner similar to the mechanisms suggested for the cause of injuries observed at stable deep depths, as discussed above. In any case, the inner ear seems to be particularly susceptible to injury during changes in inert gas composition, not only at stable deep depths, but during decompression.

McCormick *et al*,[26] in a study designed to produce experimental decompression sickness in guinea pigs, has actually observed bubble formations and hemorrhages in the labyrinth with depressions of the cochlear microphonic. Interestingly, predive treatment of the animals with heparin results in a decrease in the cochlear microphonic changes. This suggests that intravascular clotting plays a significant role in labyrinthine decompression sickness.

The following measures should be taken in regard to otologic symptoms appearing during or shortly after decompression from dives in which decompression sickness is possible and in which middle ear barotrauma is unlikely:

1. Isolated cochlear and/or vestibular symptoms during such dives should be considered forms of decompression sickness and should be recompressed promptly.

2. Divers who experience such symptoms during or shortly after a switch to an air environment during decompression from a deep helium-oxygen exposure should be switched back to the presymptom helium-oxygen atmosphere and recompressed promptly.

3. The optimum treatment depth or depth of recompression is at present unknown. Obviously, the depth at which relief of symptoms occurs would be a good endpoint. However, in some cases, bubble formations in the inner ear might

result in structural deformities, such as breaks of membranes, and prompt relief will not be seen even though an adequate depth of recompression to drive the bubbles back into solution is achieved. The optimum depth of recompression for otologic decompression sickness is theoretically the lesser of the depth of relief, or the bottom depth. Occasionally, particularly in the open sea, returning to the bottom depth may be hazardous or impractical. Therefore, we suggest that the optimum treatment depth in these situations should be at least three atmospheres (30.5 meters) deeper than the depth at which the symptoms began. Thus far, we have had the opportunity to use this treatment depth in only one case, with a successful outcome. Therefore, this recommendation is empirical, and a more precise definition of optimum treatment depths for otologic decompression sickness requires additional experience and investigation.

4. The use of other measures in the treatment of otologic decompression sickness, such as anticoagulants, low molecular weight dextran, and intermittent oxygen enriched treatment gases has not been adequately evaluated. If inner ear bubble formation has resulted in structural destruction with subsequent hemorrhages, anticoagulation might cause additional harm and should not be used. Conversely, the use of oxygen enriched treatment gases[60] during the treatment of otologic decompression sickness is less likely to cause additional harm and may be beneficial.

5. Studies by Sekitani *et al*[82] and McCabe[83] indicate that diazepam has specific effects upon the physiologic function of the central vestibular system, depresses the slow and quick phase velocities of nystagmus in labyrinthectomized cats, and is clinically useful in the symptomatic treatment of vestibular disorders. Bernstein *et al*[84] have shown that diazepam does not delay central vestibular compensation after hemilabyrinthectomy in cats. In our series, the parenteral administration of diazepam, along with prompt recompression therapy in one case, resulted in fast relief of severe vertigo, nausea, and vomiting. Until future studies indicate otherwise, the use of diazepam at pressure for symptomatic relief of divers who experience vestibular decompression sickness during dry chamber dives seems appropriate.

6. The gradual disappearance of vertigo after an acute unilateral vestibular end-organ injury over a period to two to three weeks is usually the result of compensation within the CNS and does not necessarily mean that the injured end-organ has recovered normal function. Certain motions and positions can and frequently do cause vertigo and loss of spatial orientation in individuals who have fully compensated from permanent end-organ injuries. This is especially true in underwater conditions where disturbances of vision and loss of proprioceptive inputs from buoyancy increase the difficulties of maintaining spatial orientation. Therefore, divers who experience inner ear injuries should have a complete otoneurological evaluation after their symptoms have apparently subsided. If permanent inner ear injury is found, these individuals should not return to diving.

INJURIES RELATED TO HIGH BACKGROUND NOISE DURING DIVING CONDITIONS

Previous studies[12,14,16] have indicated that neurosensory deafness in divers is related to nondiving excessive noise exposure. These reports consisted of investigations of military divers where history of excessive noise exposure in nondiving situations is more frequent. Coles and Knight,[16] in a survey of Royal Navy divers, noted that a selected subgroup of divers with no previous history of excessive noise exposure had hearing thresholds which were similar to the nondiving British population when allowances were made for age. Zannini *et al*[85] reported that professional divers demonstrated much higher instances of high-frequency hearing losses than the general Italian population. They did not attribute this to excessive noise exposure, but instead postulated that these losses were secondary to "reflex vasomotor problems."

Recent studies by Summitt and Rei-

mers[86] and Murray[87] have demonstrated excessive noise levels in pressure chambers and diving helmets. Noise levels inside helmets were found to be due to the inflow of breathing gases and ranged from levels of 98 to 112 dBA. Levels in pressure chambers with ventilation equipment running were noted to be as high as 120 dBA. Studies of chambers in our institution have revealed similar levels during compression. At stable depths with ventilation equipment running, noise levels decreased to 80-85 dBA. With the higher levels, using acceptable damage risk criteria,[38] the allowable exposure time may be as short as 15 or 20 minutes before a significant risk of noise induced hearing loss occurs. Many diving situations involving helmets or chambers result in much longer exposures. Current decompression schedules from deep depths, 152.4 meters and greater, involve decompression lasting from several days to two weeks, depending upon the depth of dive and time spent on the bottom.

Summitt and Reimers[86] measured the hearing thresholds of three US Navy divers following routine air helmet dives during which the noise levels ranged from 100 to 120 dBA. The divers reported difficulties in communication during the dives because of the background noise. Two divers showed significant temporary threshold shifts following a 57.91 meter dive for a total exposure time of 64 minutes. The third diver showed a similar temporary threshold shift following an 18.29 meter 53 minute dive. The threshold shifts ranged from 10 to 40 dB and were noted mostly at frequencies greater than 1,000 Hz. Hearing returned to predive levels within 24 to 48 hours postdive. There was no difficulty with ear clearing or evidence of barotrauma in either of these cases. Also, decompression sickness was unlikely with these dive profiles. The temporary conductive hearing losses occurring during diving, as previously noted by Fluur and Adolfson,[28] Farmer *et al*,[29] and Thomas *et al*,[30] apparently did not provide sufficient attenuation to protect these divers from the ambient noise encountered. Whether or not conductive hearing losses at deeper depths will provide sufficient attenuation or protection from excessive noise exposure requires further investigation.

These studies suggest that helmet and chamber divers are frequently exposed to noise levels which exceed the current damage risk criteria for surface exposures. Such noises are usually produced by the inflow or outflow of gases or by ventilation equipment, which during saturation dives requiring prolonged exposures, is kept running constantly in order to remove carbon dioxide and to insure an adequate distribution of oxygen. Undoubtedly, some of the high frequency hearing losses seen in the diving population are related to excessive noise exposure during nondiving conditions. However, these studies suggest that some of these losses are related to excessive noise exposure encountered during diving. Until more data is available regarding the actual damage risks from excessive noise in diving, chambers and helmets should be designed to operate as quietly as possible. If excessive noise during these conditions is likely, some type of protective attenuation such as ventilated ear muffs or plugs should be provided.

SUMMARY

Attempts to alleviate world wide energy, mineral and food shortages by utilization of undersea resources have recently resulted in more extensive commercial as well as military and sport diving. New effects have been undertaken to devise means of safely exposing humans to deeper depths. Inner ear disturbances during these adverse environmental exposures have been encountered with increasing frequency. To prevent and treat these problems, otolaryngologists and the diving community must gain a better understanding of inner ear physiology and pathology in compressed gas environments.

Studies of hearing in humans exposed to simulated depths of up to 305 meters have not shown, thus far, any evidence of cochlear dysfunction in the absence of otic barotrauma or decompression sickness. Reversible, depth related, con-

ductive hearing losses have been noted. These changes are apparently due to an increase in the impedance of the middle ear transformer in dense gas environments and to changes in the middle ear resonance frequency in helium.

Transient vertigo and nystagmus during diving have been noted when cold water enters external ear canals in unequal amounts due to obstruction of one canal by cerumen, otitis externa, ear plugs, or bony exostoses. Transient vertigo and nystagmus have also been demonstrated with unequal middle ear pressure equilibration during ascent and descent (alternobaric vertigo).

Transient symptoms of intention tremor, dizziness, nausea, plus decrements in standing steadiness and psychomotor performance (the high pressure nervous syndrome or HPNS) have been described in humans during rapid compression in helium-oxygen atmospheres at depths greater than 152.4 meters. The mechanism of these symptoms is not known. However, ENG studies during HPNS have shown no evidence of vestibular end-organ dysfunction. A decrease in cerebellar function, similar to observed EEG changes in cortical function in compressed gas environments, is postulated to explain the dysequilibrium and tremor of the HPNS. Future studies are needed to better understand this phenomenon.

Persistent cochlear and vestibular damage has been noted during several phases of diving: during compression, at stable deep depths, and during decompression.

Such injuries occurring during compression appear to be related to round window ruptures associated with inadequate middle ear pressure equilibration during descent. A Valsalva's maneuver or straining causes an increase in CSF pressure which can be transmitted to the perilymphatic space through the cochlear aqueduct. With an already existing negative middle ear pressure from inadequate ear clearing during compression, this sudden rise in perilymphatic pressure results in a greater pressure differential between the middle and inner ear, and rupture of the round window membrane can occur. Eleven cases of round window fistulae related to diving have been reported. Most of these cases occurred with shallow dives in which decompression sickness was not a factor. While ruptures of the oval window annular ligament with diving have been, thus far, not reported, these injuries have been seen with sudden hearing losses related to nondiving stresses, and thus, should also be considered as a cause of inner ear injury during the compression phase of diving.

Divers who suffer inner ear symptoms with dives in which decompression sickness is unlikely, should be suspected of having a labyrinthine window fistula. They should be placed on bed rest with head elevation and avoidance of coughing, straining, or other maneuvers which result in significant increases in CSF pressure. Hyperbaric oxygen therapy would seem contraindicated in these cases, for recompression subjects the diver to the same pressure changes which produced the injury.

Labyrinthine vestibular damage has been noted in three divers after changes in inspired inert gases while at stable deep depths. The mechanism of these injuries is not known. Intralabyrinthine fluid shifts secondary to differences in osmotic pressure between the perilymphatic and endolymphatic spaces, or bubble formations at Reissner's membrane due to counterdiffusion between the perilymph and endolymph of the two dissolved, inert gases, are postulated to occur during these conditions. These injuries should be preventable by avoiding inert gas exchanges at deep depths.

Permanent inner ear damage with hearing loss, tinnitus, and/or vertigo can be the only manifestation of decompression sickness, particularly after deep helium-oxygen diving in which a change in inert gases has occurred during the latter stages of decompression. In a series of 23 such cases, a significant correlation is apparent between prompt recompression treatment, relief of symptoms, and lack of residual deficits. Other measures which might be useful and not harmful in the management of otologic decompression sickness include paren-

teral diazepam for symptom relief and cyclic inhalations of oxygen enriched treatment gases. The optimum depth of recompression treatment is not known. Until future studies indicate otherwise, divers with otologic decompression sickness should be promptly recompressed to at least three atmospheres (30.17 meters) deeper than the symptom onset depth. When these injuries occur with or shortly after an inert gas switch during the latter stages of decompression, recompression should be accomplished using the helium-oxygen mixture present before the switch.

Divers who suffer inner ear injuries should have a complete otoneurological evaluation. Those who exhibit permanent end-organ injury should not return to diving.

Excessive background noise has been described during various diving conditions and has been associated with temporary threshold shifts in helmet divers. Until appropriate damage risk criteria in compressed gas environments are devised, diving helmets and chambers should be designed to operate as quietly as possible, or protective attenuation by ventilated ear muffs or plugs should be used.

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REPRINTS — Joseph C. Farmer, Jr., MD, Div. of Otolaryngology, Dept. of Surgery, Duke University Medical Center, Durham, NC 27710.

ABSTRACT

Farmer, J.C., Jr. and W.G. Thomas

Auditory and vestibular function in diving.

In: Bennett, P.B. and D.H. Elliott. The physiology and medicine of diving and compressed air work; Second Edition, p. 522-544. Baltimore, Williams and Wilkins Co., 1975.

The most frequent problem is associated with difficulties with middle ear pressure equalization. The subsequent creation of a pressure differential between the middle ear and the ambient environment can lead to transient cochlear and/or vestibular dysfunction or to more serious permanent problems related to the inner ear damage. During diving in which there is no apparent difficulty with middle ear pressure equalization, divers develop a reversible conductive hearing loss which is related to depth and gas mixture. This loss is apparently secondary to changes in gas density, resonance shift, and subsequent impedance mismatches between the surrounding environment and the inner ear. . . . Various alterations during multiple phases of diving can lead to transient cochlear and/or vestibular dysfunction or permanent injury. It can include such pathological changes as rupture of the round window membrane, as seen during compression; the formation of gas bubbles in the intracochlear spaces as postulated to explain those injuries occurring at stable deep depths but associated with changes in inert gas composition; the formation of intravascular gas or platelet emboli in the arterial supply or venous drainage or gas bubbles in the intracochlear fluid spaces during decompression, or possible hair cell damage secondary to excessive noise exposure. Possible direct alterations in the inner ear resulting from high inert gas concentrations might inhibit active or passive ion transport or result in fluid electrolyte changes. (From authors' summary)

IN: Aerosp. Med. 57:783–785; 1966.

Hearing in Hyperbaric Air

ERIK FLUUR, M.D., and JOHN ADOLFSON, PH.D.

The effect of increased ambient air pressure on the hearing function in 26 experienced divers was investigated. Air and bone conduction audiograms were made in normal air (1 ata) and in hyperbaric air (4, and 7, and 10, and 11 ata). After correcting for the transmission changes in the earphone (5-10 dB), the maximum elevation of the hearing threshold was found to be about 30-40 dB in the middle frequency range of hearing. The bone conduction was unaffected.

THE ACOUSTIC COMMUNICATION between the surface and the divers has long been a problem of outmost importance for navies in all countries. The increased ambient pressure at great depths—between 30 and 120 meters—causes changes in the diver's ability to talk and to comprehend speech. These changes are brought about by many factors. The increased partial pressure of oxygen, nitrogen and carbon dioxide affects the consciousness; consequently the diver has difficulty in obeying given orders.[1,2,3,5,6]

In 1898, Lester and Gomez[5] observed diminution in auditory acuity of eight subjects in a caisson of the East River bridge construction. The investigators concluded that both air and bone conduction of sound were considerably reduced while under pressure of 3 and 3.5 ata (atmospheres absolute). This diminution was proportional to the rise in atmospheric pressure. The effect persisted for 24-48 hours after leaving the caisson.

Other investigators have found that divers very frequently have diminished hearing ability.[4,7,9]

BACKGROUND

Normally the air pressure on both sides of the tympanic membrane is equal and balance is maintained by passage of air into the middle ear via the Eustachian Tube. This equalization mechanism can function independent of the magnitude of the ambient pressure, thereby preventing the pressure to restrict the mobility of the tympanic membrane with a decreased hearing acuity as a consequence. A considerable change in the air pressure can, however, be expected to affect the

From the Department of Otolaryngology, Karolinska Sjukhuset, Stockholm 60, and The Psychological Laboratory, University of Göteborg, Göteborg.

sound perception in other ways, either through changes in the ability of the middle ear mechanism to transmit sound to the inner ear, or by affecting the round window membrane which would react upon the endolymph movements in the cochlea.

In order to elucidate this problem, an investigation was made at the Laboratory for Aviation and Naval Medicine, Karolinska Institutet, and at the Naval Diving Training Center in Stockholm, Sweden. The scope was: 1, to determine the changes of the sound transmission properties of the audiometric earphones when exposed to increased static pressure and 2, to determine changes in the hearing thresholds as recorded by air and bone conduction tone audiometry, at different ambient pressures.

EQUIPMENT AND ACOUSTIC MEASUREMENT

The measurements were made in a pressure tank in which the static pressure could be raised up to 11 ata. For the audiometric investigations the air and bone conduction receivers and a signal button were placed inside the tank, and the audiometer and operator outside. The hearing threshold determinations were for the air conduction tests carried out with earphones (TDH-39 with MX 41 AR Cushions) and for the bone conduction test with a traditional audiometric bone conductor receiver. The tone audiometry (Tegnér T2) was calibrated according to British Standard nr 2497 (1954). During the hearing measurements the noise level in the tank was judged to be sufficiently low not to affect the results of the measurements.

As the changes in the static pressure could be expected to influence on the transmission properties of the used earphones an analysis of these circumstances was first carried out. Frequency response measurements were made at three different pressures (4 and 7 and 11 ata) using an artificial ear of 6 cc cavity (ASA Bruel and Kjaer) (Figure 1).

In evaluating these results a correction was introduced for the influence of static pressure changes on the condensor microphone in the artificial ear used according to information given by the manufacturer. After application of the correction figures the earphones showed a frequency response as a function of different pressures as shown by Figure 2.

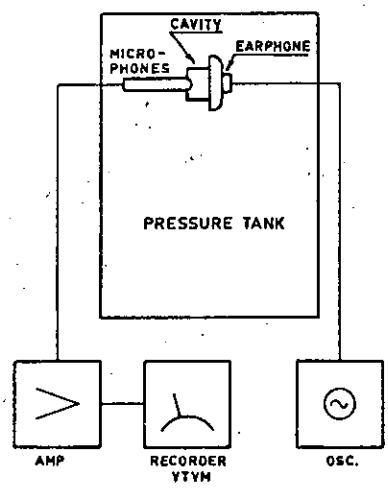

Fig. 1. Connection scheme of the measurement instruments.

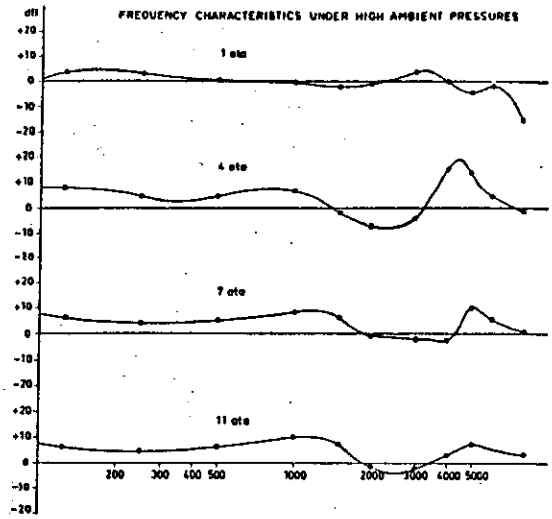

Fig. 2. Frequency responses from the earphone type TDH 39, 6 ccm cavity, under high ambient pressure.

THE AUDIOMETRIC INVESTIGATION

Material and methods—The audiologic investigation, consisting of conventional air and bone conduction audiometry in the frequency range of 250-6000 cps, was made on 26 experienced divers. In order to detect any harmful effect of the slight noise level in the tank, an audiogram was taken under silent environmental conditions the day before the experiment. No significant changes were observed and the audiometric conditions were therefore judged satisfactory. During the experiment, the subjects were freely breathing chamber air (without mouth piece). The pressure inside the chamber was then raised to 4, 7, 10 (6 subjects), and 11 (20 subjects) ata. A complete audiogram was taken once on each pressure level, and once again as these levels were reached in the descent of pressure.

As a further control this experiment procedure has been repeated on six of the subjects.

RESULTS

Exposure to increased ambient pressure has produced with very small variations, the same reduction of hearing acuity for air-conducted sound in all subjects. Within the frequency range tested the hearing threshold curve for air conduction at 11 ata was elevated 20-30 dB (Figure 3). For the two highest test frequencies the elevation was less marked, generally only 10 dB. The subjects which before the experiment showed good hearing at these frequencies demonstrat-

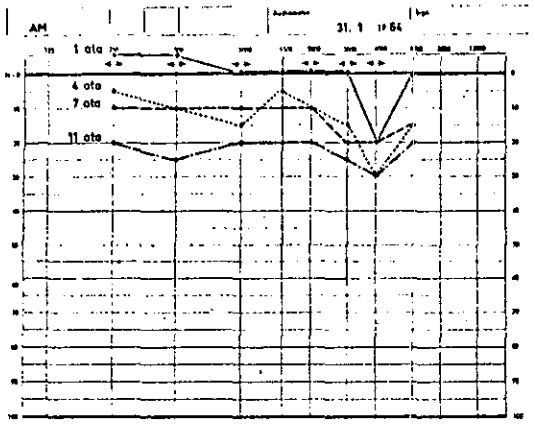

Fig. 3. Example of a conduction threshold at different pressures.

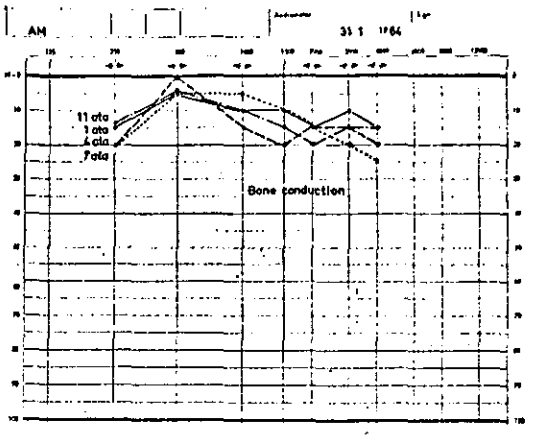

Fig. 4. Example of bone conduction threshold at different pressures. The deviation shown has to be accepted as insignificant for this mode of measurements.

ed only insignificant changes here, in most cases within ±5 dB.

Taking into account the increase in sound pressure from the earphones caused by the raise of the static pressure points toward an even higher degree of threshold elevation.

The bone conduction thresholds were unaffected by changes in the ambient pressures as shown in Figure 4.

The hearing threshold curves—air and bone conduction—for the six subjects which were investigated at two different occasions were in close agreement on both experiments.

DISCUSSION

This investigation has shown that divers demonstrate an elevation of the threshold of hearing for air conducted sound which increases with increasd ambient air pressure. However, the bone conduction threshold which is considered to reflect the function of the inner ear perceptive mechanism remains unaffected.

CONCLUSION

Apart from physical changes in the transmission characteristic of the communication system the diver's hearing difficulties to some extent may be explained by the fact that the increased ambient pressure causes disturbances of sound conduction through the middle ear. The unaffected bone conduction thresholds indicate that no loss of sensitivity appears in the sensory-neural function.

SUMMARY

The aim of this investigation was to determine the effect of increased ambient pressure on the hearing function in divers. To enable a correct evaluation of the results of psycho-acoustic hearing measurements a thorough investigation of the changes in the transmission characteristics of the transducers as a function of air pressure was performed. Air and bone conduction audiograms were made on 26 experienced divers in normal air (1 ata) and in hyperbaric air (4, 7, 10 and 11 ata). After correcting for the transmission changes in the earphone (5-10 dB), the maximum elevation of the hearing threshold was found to be around 30-40 dB in the middle frequency range of hearing. The bone conduction, however, was unaffected.

This investigation has been supported by grants from the Delegation for Applied Defence Research, Ministry of Defence, Stockholm.

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ABSTRACT

FREEMAN, P. and C. Edmonds.

Inner ear barotrauma.

Arch. Otolaryngol. 95:556-563; June 1972.

Five patients demonstrated a sensorineural hearing defect following aural barotrauma. Preincident and postincident audiograms show the extent of impairment to vary from a high frequency loss to a total sensorineural deafness. The men involved were all Navy divers and they all experienced difficulty in clearing their ears on descent. The terminology recommended for this condition is "inner ear barotrauma," to differentiate it from other forms of barotrauma and from the involvement of the eighth nerve in decompression sickness. (Authors' abstract)

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A new gas lesion syndrome in man, induced by "isobaric gas counterdiffusion"

C. J. LAMBERTSEN AND J. IDICULA
Institute for Environmental Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania 19174

LAMBERTSEN, C. J., AND J. IDICULA. *A new gas lesion syndrome in man, induced by "isobaric gas counterdiffusion."* J. Appl. Physiol. 39(3): 434–443. 1975.—Normal men have been found to develop pruritis and gas bubble lesions in the skin, and disruption of vestibular function, when breathing nitrogen or neon with oxygen *while surrounded by helium at increased ambient pressure*. This phenomenon, which occurs at stable ambient pressures, at 1 or many ATA, has been designated the "isobaric gas counterdiffusion syndrome." In a series of analyses and experiments in vivo and in vitro the cause of the syndrome has been established as due to gas accumulation and development of gas bubbles in tissues as a result of differences in selective diffusivities, for various respired and ambient gases, in the tissue substances between capillary blood and the surrounding atmosphere. The phenomenon here described in man is an initial stage of a process shown later in animals to progress to continuous, massive, lethal, intravascular gas embolization.

inert gases; diving; counterdiffusion; bubbles; decompression sickness; isobaric gas counterdiffusion syndrome, vertigo; skin; vestibular function; ear; neon; helium; nitrogen

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THIS PAPER DESCRIBES the identification in man of a newly recognized gas lesion disease, occurring as an evolution of gas in skin and other sites, associated with vestibular dysfunction, and potentially producing lethal gas embolization (20, 21). The gas bubble lesions and symptoms developed when the gas respired by normal men contained one inert gas (*nitrogen or neon, with normal oxygen*) while the subjects were surrounded by another inert gas (helium with normal oxygen), at increased but stable elevated ambient pressures (11, 12, 21). Dermal itching developed, followed by generation of gross, gas-filled lesions in skin exposed to the helium environment, and also by abrupt onset of vestibular dysfunction. Incapacitation resulted from either the effects of itching alone or the effects of the sustained vertigo and nausea associated with disruption of vestibular function.

The composite dermal-vascular-vestibular syndrome has been designated by this present description and cited in our separate discussion of its theoretical basis (11, 12), as the "Isobaric Gas Counterdiffusion Syndrome." By this designation the pathophysiological consequences of gas counterdiffusion, even at the same, unchanged ambient pressure, are implied.

Some of the pathophysiological phenomena to be described here were encountered previously by others in laboratory experiments (3) and very probably have led to serious accidents and death in practical diving (personal communication in open-sea diving accidents) but were not previously recognized as due to evolution of a gas bubble phase in tissues. The description which follows is concerned with the detailed observations of the lesions in man, and their initial recognition as being induced by gas bubble formation occurring in tissues without change in ambient pressure. The conditions which produced the pattern of pathological changes are described and related to the specific investigations then utilized to further establish the manner of occurrence of gas lesions in in vivo and in vitro systems in the "isobaric state." The initial theoretical analysis of this condition, derived following these observations in man, has been presented elsewhere (11, 12).

Background—Nature of Previous Studies

Development of cutaneous lesions in association with studies of undersea physiology has previously been observed. One well-known form of lesion is that related to too rapid decompression after exposure to elevated inert gas pressures (1, 6, 27). This lesion is considered a form of skin "bends" and, while not well investigated, is probably somehow produced by gas bubbles forming locally in skin and subcutaneous tissues.

A second form of skin lesion was observed by Blenkarn et al. (3) in subjects breathing nitrogen or neon with oxygen during a prolonged stay in a helium-oxygen environment within a chamber at a stable ambient pressure equivalent to 200 ft of seawater (7 ATA). These lesions, called urticarial type eruptions by the observers, were further described as erythematous and maculopapular, with scattered petechiae, and areas of purplish-blue discoloration with surrounding blanching or mottling. Headache and blurred vision were also cited as occurring in association with the skin lesions in these episodes. The observers recognized that the dermal lesions must be related to some physical characteristics of the inert gases breathed. However, they deduced that the rapid diffusion rate of helium within and and *from* body tissues when another, less-diffusible inert gas was administered would lead to a fall in tissue total inert gas pressure (e.g., the sum of He and N_2 partial pressures). Postulating that the skin lesions observed could therefore not be attributed to evolution of gas bubbles they proposed that the dermal lesions were produced by a *mechanism* involving water fluxes in skin, the movement of

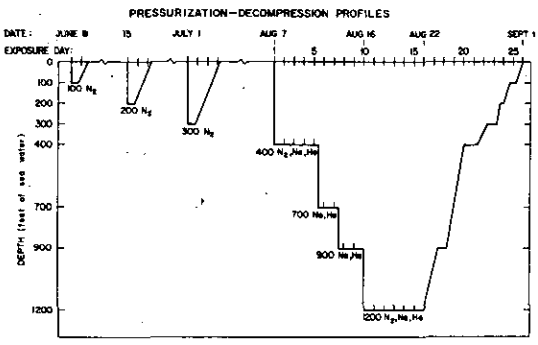

FIG. 1. Sequence of exposures to increased pressure in an environmental chamber system. Ambient gas at 100 ft of seawater was N_2 with natural P_{O_2}. At all other depths ambient gas was He with natural P_{O_2}. Gases breathed differed from ambient gas during part of each experiment day.

TABLE 1. *Correlation of depth in seawater to hydrostatic pressure (rounded values)*

Seawater Depth		Absolute Pressures		
ft	m	ATA	lb/in²	mmHg
100	30.5	4.0	59.2	3,063
200	61.0	7.1	103.8	5,366
300	91.4	10.1	148.3	7,669
400	121.9	13.1	192.8	9,972
700	213.4	22.2	326.4	16,881
900	274.3	28.3	415.5	21,487
1200	365.8	37.4	549.1	28,396

water being induced osmotically by concentration gradients of dissolved gases (14, 15).

Specific reduplication of the above described exposures (3) which had led to dermal lesions was performed in another laboratory, but no lesions developed (personal communication concerning study at US Navy Experimental Diving Unit, 1971). It was therefore here considered reasonable to proceed with this Institute's planned Predictive Studies series of experiments involving alternating exposure to different inert gas atmospheres at extreme increased ambient pressures (19).

FACTORS AND CIRCUMSTANCES LEADING TO DEVELOPMENT AND IDENTIFICATION OF GAS LESIONS

The phenomena comprising the isobaric inert gas counterdiffusion syndrome occurred in the course of the third in a series of collaborative studies of the limits of human tolerance to increased pressures of respiratory and ambient gases (19). This study involved prolonged exposure of four normal subjects to a series of high ambient helium pressures (equivalent to 100, 200, 300, 400, 700, 900, and 1,200 ft of seawater), during which physiological and other effects of respired gas mixtures containing nitrogen, neon, or helium with natural oxygen pressure were examined.

The pattern of exposures, designed to provide comparative, "dose-response" information for acute exposure to nitrogen, neon, and helium is indicated generally in Fig. 1. Equivalent pressures expressed as atmospheres absolute, millimeters of mercury, and feet of seawater are shown in Table 1. Through these exposures it was intended to increase inspired gas density, mimicking pulmonary and respiratory work stresses equivalent to those to be expected with helium breathing at depths to 2,000, 3,000, 4,000, and 5,000 ft of seawater, while also investigating neurophysiological, mental, sensory, hematological, and other effects of graded increase in pressure of these inert gases. These studies were conducted because it had already been demonstrated that small animals could remain conscious in a helium-oxygen atmosphere at pressures greater than 122 ATA (equivalent to 4,000 ft of seawater) and survive decompression from such exposures (24, 25).

Conditions for the basic investigative purposes described included:

a) Saturation or near-saturation exposure to helium as the respired gas, with high tissue helium partial pressures induced by multihour or multiday residence in the chamber atmosphere of helium with natural inspired oxygen pressure (0.2 ATA).

b) Periodic substitution of a respired gas mixture from a source different from the ambient chamber atmosphere. The respired gases, all with natural inspired oxygen pressure, included nitrogen-oxygen, nitrogen-helium-oxygen, neon-helium-oxygen, or helium-oxygen mixtures (Figs. 2 and 3). The duration of this substitution ranged from about 30 to about 70 min, with abrupt onset and abrupt return to respiration of chamber helium-oxygen atmosphere.

The substitutions occurred at rest, in conditions of stepwise increase in exercise to extreme levels of work, and during administration of carbon dioxide to determine respiratory reactivity.

c) Situations with exposure to more than one additional inert gas (nitrogen and neon) sequentially in the same day, interspaced with return to respiration of chamber helium with oxygen as the base-line or "escape" atmosphere.

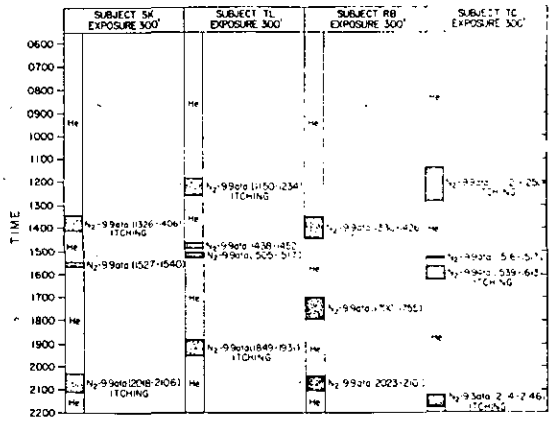

FIG. 2. Relation of symptoms to sequence of changes in respiratory gas and to duration of isobaric counterdiffusion. Sequences for each subject are those experienced at 300 ft of seawater. Narrow vertical columns indicate order of gas administration. Wide vertical columns show pressure and duration of counterdiffusion and symptoms encountered. Numbers in parentheses indicate exact timing of counterdiffusion.

In the course of these many exposures, cutaneous itching was encountered at all pressures from 200 to 1,200 ft of seawater, with vestibular dysfunction occurring only during exposure equivalent to 1,200 ft of seawater.

SEQUENCE OF OBSERVATIONS—
ISOBARIC COUNTERDIFFUSION GAS LESION SYNDROME

Pruritis

The initial observation of abnormality associated with counterdiffusion occurred at 200 ft of seawater pressure equivalent, in *subject TC* breathing 97% N_2 with 3% O_2 (i.e., normoxic) in a partial rebreathing system, together with autogenous CO_2 accumulation to 50 mmHg in the inspired gas mixture. Extreme, eventually intolerable pruritis of legs, arms, and trunk, together with the combined stresses of hypercapnia and nitrogen narcosis, made premature termination of the experimental exposure necessary after 40 min. Direct examination of the skin by one of us (*CJL*) at the increased ambient pressure during and immediately following exposure to nitrogen breathing revealed no evidence of dermal lesions or other indications of dermal change. This phenomenon of itching without visible lesions occurred in three of the four subjects at the 200-ft pressure equivalent (Table 2). It was judged at that time that the pruritis was an example of the undiagnosed condition noted by Blenkarn et al. (3) and to control it, gastight body suits with neck and wrist seals were devised to surround trunk and limbs and were ventilated with the gas respired to minimize the surface area exposed to the ambient helium environment. These suits (Fig. 4) discharged their ventilating "respiratory" gas to outside the chamber to avoid contaminating the helium-oxygen atmosphere of the environmental chamber system itself. By their use, exposure of the body surface to chamber helium was limited to hands, scalp, ears, eyes, upper face (above the aviation-type oronasal mask or mouthpiece used for respiratory gas administration), and a small area of skin surface on the neck. Mucosal surfaces of the nose and mouth were exposed only to the gas breathed. By this means of limiting the surface area where itching occurred the highly motivated subjects were able to tolerate the full periods of respiratory gas substitution required for the studies being performed. When pruritis became extreme on the scalp or other exposed locations, only cooling by ice bags was used to help alleviate the discomfort. This limitation was imposed to avoid possible aggravation of skin lesions by chemical antipruritics.

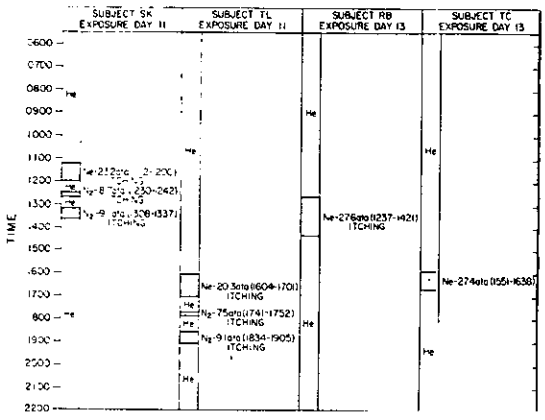

FIG. 3. *Exposure days 11* and *13*. Ambient He-O_2 pressure in chamber is equivalent to 1,200 ft of seawater. Narrow vertical columns indicate order of breathing N_2, He, or Ne. Wide vertical columns show pressure and duration of counterdiffusion, and symptoms encountered. Numbers in parentheses indicate exact period of counterdiffusion exposure.

Dermal Lesions

Different distinct types of dermal lesions appeared on exposed skin as the use of suits permitted more prolonged respiratory exposure to gas mixtures containing nitrogen or neon. Under close inspection each was considered *not* to be typical of allergic urticarial lesions and *not* to be inflammatory in the development phase. One form (*subject TL*) began as a localized group of raised, opaque, white, hard lesions, which grew in size to become a confluent mass of papules (Fig. 5). The opaque white character of the mass without surrounding erythema was considered to be due to a physical process, generated by development of gas spaces within the skin, the pressure of the contents of the expanding lesion displacing blood from the lesion itself and from immediately adjacent tissue. Erythematous response, absent during development and existence of the raised lesion mass, was observed but minimal at the site where a lesion had

TABLE 2. *Circumstances of occurrence of symptoms and lesions—subjects in isobaric gas counterdiffusion*

Pressure Equivalent to ft of Seawater	Chamber Gas	Gas Breathed	*Subject SK*			*Subject RB*			*Subject TC*			*Subject TL*		
			Pruritis	Dermal lesions	Vertigo	Pruritis	Dermal lesions	Vertigo	Pruritis	Dermal lesions	Vertigo	Pruritis	Dermal lesions	Vertigo
100	N_2	N_2	—	—	—	—	—	—	—	—	—	—	—	—
200	He	N_2	x	—	—	—	—	—	x	—	—	x	—	—
300	He	N_2	x	x	—	—	—	—	x	x	—	x	x	—
400	He	N_2	x	x	—	x	—	—	x	—	—	x	x	—
	He	Ne	—	—	—	—	—	—	x	—	—	—	—	—
700	He	Ne	—	—	—	—	—	—	x	—	—	—	—	—
900	He	Ne	x	—	—	—	—	—	x	—	—	x	—	—
1,200	He	N_2*	x	—	x	o	o	o	o	o	o	x	x	—
		Ne	x	—	—	x	—	x	—	—	x	x	—	—

Symbols: o = gas not breathed; — = effect did not occur; x = effect did occur. * N_2 pressure equivalent to 10 ATA (300 ft of seawater).

FIG. 4. Subjects wearing ventilatable suits which protected torso and limbs from itching during respiration of N_2 or Ne while surrounded by He. No skin lesions had been seen prior to use of the suits, probably because severity of itching over large body surface areas made continued counterdiffusion intolerable. More severe lesions developed in smaller areas of exposed skin surface when trunk and limbs were protected by the suits.

existed, persisting over a period of approximately 1 h after the return to helium breathing led to resolution of the lesion.

Dissection of this form of lesion, which occurred at the pressure equivalent to 1,200 ft of seawater, was carried out with a needle by a subject under direct, magnified inspection by one of us (*CJL*). The dissection revealed subepithelial tissue from which neither blood nor watery fluid was obtained as the opaque white papules were disrupted. The appearance was considered that of numerous, tightly packed, confluent gas spaces, rather than that of extravasation of fluid. Since the dissection was not conducted with the lesion under water, it was not possible to identify escaping gas, as was subsequently found possible during experiments in the pig.

The second form of lesion, characteristic of those which tended to occur in a second subject (*SK*) involved multiple, diffusely scattered, discrete, raised, nonconfluent, opaque white papules, essentially the same in appearance as the larger lesions described above, except for the smaller size and scattered locations. These covered much of the exposed facial area (Fig. 6).

A third subject (*TC*) tended to develop pruritis without the actual occurrence of gross lesions during the limited periods of counterdiffusion exposure.

The fourth subject (*RB*) tended not to develop pruritis or lesions even though his exposure to nitrogen and neon as breathing gases in counterdiffusion was equivalent to that of the others.

The pruritis and dermal lesions regressed and disappeared on return to breathing the chamber atmosphere of helium with normal oxygen pressure. No therapy was employed to hasten resolution. While observations could not accurately define the time course of regression, at the 1,200-ft pressure level return to helium breathing resulted in no evident immediate change in the dermal lesions. These tended to persist, then after a lag of about 30 min, regression was noticeable. Complete disappearance of the raised papules occurred within about 40 min, but subsequently slight redness persisted at the site of the previous lesion during most of a succeeding hour. No lasting changes occurred, even with repeated development of dermal lesions.

Vestibular Dysfunction

In three of the four subjects vestibular dysfunction occurred during the period of residence at the pressure equivalent to 1,200 ft of seawater (22). It did not occur at the lower ambient pressures which served as conditions for prior phases of the study. In two subjects severe nausea, vomiting, and incapacitation by vertigo developed during actual periods of breathing nitrogen or neon. These subjects were then unable to remain erect or tolerate head movement during a several-day period of recovery. In the third subject the existence of a much less severe but nevertheless handicapping degree of vertigo and nausea (without vomiting) was identified more than 1 h after cessation of neon breathing. Since these episodes in the different subjects occurred more than a day apart and had never previously been described as a phenomenon of pressure exposure without decompression, the first instance of vertigo was not immediately suspected as having a relation to the dermal lesions and to isobaric gas counterdiffusion. It was instead considered probable that the occurrence in the first subject to be affected was of infectious (viral) origin (5, 22, 24, 29). Subsequently, after intensive examination of this possibility, the concept of an infectious basis for the vestibular derangement was discarded (22).

Differences among Subjects

Only four subjects were exposed to gas counterdiffusion and, since it was not a previously recognized cause of gas bubble lesions, specific study of the isobaric gas counterdiffusion phenomenon was not part of the initial experiment program design. Considerable useful information can nevertheless be derived by comparison of the different effects induced in the different subjects.

First, susceptibility to dermal and vestibular effects of gas counterdiffusion differed among the members of the subject group. The one subject who did not develop vestibular dysfunction (*TL*) did develop the most prominent dermal lesions. The one subject who generated no visible dermal lesions (*RB*) did experience multiday incapacitation due to vestibular dysfunction.

Representative patterns of gas administration to the subjects at two different ambient pressures (equivalent to 300 and 1,200 ft of seawater) are illustrated in Figs. 2 and 3. Complete information for each of the more than 50 acute exposures to gas counterdiffusion is provided in the data deposited in the Documentation Center (22). Specific observations concerning individual subjects include the following.

Subject RB. This black subject demonstrated almost no dermal response to gas counterdiffusion. He had itching (with no lesions) only once with nitrogen breathing, of only slight degree, only at the highest pressure of nitrogen breathed (400 ft of seawater) and then only after multiple exposures on the same day.

He had itching only once with neon, only at the highest


FIG 5


FIG. 6

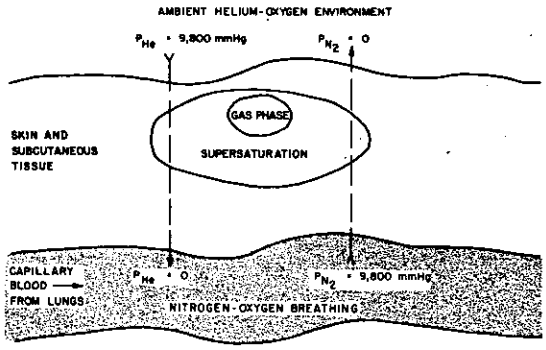

FIG. 7. Dermal gas lesions in isobaric gas counterdiffusion. Diagrammatic representation of isobaric gas counterdiffusion, with opposite gradients of He and N_2 between ambient atmosphere and capillary blood.

neon pressure exposure, without visible lesions, and only after the longest duration of neon breathing (over 70 min). This itching disappeared during exercise. It occurred 2 days before he developed the incapacitating vertigo with a shorter (39 min) and a slightly lower neon exposure. He did not have vestibular symptoms while itching existed.

Subject TC. Breathing nitrogen prior to using body suits, this white subject had prominent generalized itching at 200 ft. This occurred in a third exposure to nitrogen in that day and began very early (within 40 min of beginning the third period of nitrogen breathing). This has here raised the possibilities *a*) that bubbles already existed in the skin at the time the third nitrogen breathing period began, *b*) that both an interval of helium breathing and the subsequent exposure to nitrogen could lead to their further growth, and *c*) that bubbles may be induced and exist in a gas counterdiffusion exposure without inducing detectable symptoms.

Breathing neon this subject did not develop pruritis at the 1,200-ft pressure equivalent. However, he was the only subject in whom nitrogen induced pruritis at 400 ft and this followed two exposures to neon during that day.

Subject TL. This white subject was characterized by the most prominent conglomerate dermal lesions (Fig. 5), as well as the failure to generate vestibular derangement.

During nitrogen breathing his pruritis developed early and was extreme in degree. Actual gross lesions of forehead, cheeks, and external ears occurred at the 300- and 400-ft pressure equivalents and during 8.8 ATA N_2 breathing at the 1,200-ft ambient pressure equivalent.

Subject SK. The pattern for this white subject, who experienced the same gas exposures as *subject TL* and who developed severe vestibular derangement, was almost identical to *TL* in occurrence of dermal symptoms, but distinctly different in the character of the lesions. Like *subject TC* he had a shorter lag in onset of itching on a second nitrogen exposure. However, the second exposure was 5 h after the first.

With neon he was the only subject who developed dermal lesions at the 1,200-ft pressure level.

DISCUSSION

The preceding presentation has been descriptive of pathophysiological changes and the circumstances in which these have occurred. The intent in the following discussion is both to aid general understanding of the implications of these previously unrecognized gas lesion phenomena and to stimulate study by others. This aim will be sought by describing probable mechanisms, by correlating advance information derived from this Institute's ongoing investigations of the isobaric gas counterdiffusion process, and by elaborating circumstances in which isobaric gas counterdiffusion occurs in practical circumstances.

Counterdiffusion Concept

The concept that gas bubble formation could occur during counterdiffusion of different gases at a fixed ambient pressure developed during the period of actual exposure of individuals to different respiratory and ambient inert gases. The concept visualized at that time is illustrated in Fig. 7. At a high ambient pressure, such as in the 400 ft of seawater (13 ATA) phase of the composite study, breathing nitrogen with 0.2 ATA of inspired oxygen lowers helium pressure in the lungs and, hence, in arterial blood, toward zero. This blood, entering cutaneous capillaries, is one extreme of a gradient of helium pressure across the skin from ambient gas to capillary. In the example presented this gradient is 9,800 mmHg or close to the full 13 ATA to which the individual is exposed. Simultaneously, in the opposite direction (from capillary blood to ambient atmosphere) a nitrogen partial pressure gradient of the same magnitude exists. It was conceived that these large gradients, which can be still greater at higher ambient pressures, would lead to significant movement of each gas along its diffusion gradient. The magnitude of such movement is evidently greater than has previously been appreciated, although some measurements exist from which the probable flux (volume per unit time per unit area) can be estimated. Klocke et al. (18) have measured helium, nitrogen and oxygen transfer across the 1,025-cm^2 area of forearm and hand skin. At approximately 37°C and at atmospheric pressure they obtained values of 4.22 ml/h per 760 mmHg for helium and 2.59 ml/h per 760 mmHg for nitrogen (18). These values can be converted to represent transfer of approximately 40 ml helium/h per ATA per m^2 body surface, as compared with approximately 25 ml for nitrogen. Further, for total cutaneous gas exchange under such conditions in a large adult human of nearly 2 m^2 of surface area, the volume diffusing through skin would be approximately twice this, or 80 and 50 ml/h per ATA, respectively. Therefore, at the 13-ATA pressure of the example cited above, thirteen times the flux would be expected, and a gas flow equivalent to over 1,000 ml of helium at 1 ATA should "counterdiffuse" per hour with approximately 700

FIG. 5. *Subject TC*, with raised confluent lesion on cheek. Similar lesions developed concurrently in an eyebrow and on the pinna of the ear. Cover on head is ice bag used to suppress itching of scalp.

FIG. 6. *Subject SK*, with scattered raised lesions on forehead and face.

ml of nitrogen. At 37 ATA these values should approximate the amazing volumes of 3 liters of He and 2 liters of N_2, respectively. It was therefore considered that small differences in flux rates of gases involved in the counterdiffusion process could lead to gas accumulation, bubble formation, and the observed lesions. In the presence of gas nuclei or actual bubbles it was also considered that the counterdiffusion process could lead to growth of existing gas phases.

Prediction of Counterdiffusion Supersaturation and Test of Concept in Physical Systems

A next step in the development of the isobaric counterdiffusion gas lesion concept involved mathematical test and expression of factors involved. With Graves and Quinn, it was calculated that, when two gases counterdiffuse in the appropriate directions through two adjacent membranes having different ratios of permeability for the two gases, the sum of the partial pressures of the gases at the interface will exceed the ambient pressure driving the gases through the membranes (11, 12). This analysis in part resembles the circumstances in chemical engineering described by Brian et al. (4) of gas supersaturation developing in bulk liquids exposed to conditions of simultaneous gas absorption and desorption. In stable-state counterdiffusion across membranes it was estimated that, for optimum circumstances, the counterdiffusion mechanism is theoretically capable of generating an inert gas supersaturation to levels as great as 26% of ambient pressure (12). As shown in Fig. 8, *this means that at 1,200 ft of seawater (37.4 ATA, 28,000 mmHg) the breathing of neon with normal oxygen while surrounded with helium should lead to localized stable state excess inert gas pressures (supersaturation) as great as 9.7 ATA or 7,300 mmHg.* These entirely theoretical estimations are approximately 200 times the inert gas supersaturation considered large enough to induce bubble formation in decompression after diving. Even expecting the inevitable lateral diffusion of gases from a punctate region of extreme supersaturation to reduce this almost inconceivable supersaturation, such excess of gas partial pressures at discrete microscopic sites must inevitably lead to bubble formation and bubble growth unless all nuclei have previously been eliminated by extreme pressurization (8). These predicted massive supersaturation pressures are also to be contrasted with the approximately 0.9 mmHg maximum pressure estimated to be generated by the gas-induced osmosis previously proposed as a basis for pruritis and dermal lesions during nitrogen breathing at 200 ft of seawater in a helium ambient environment (14).

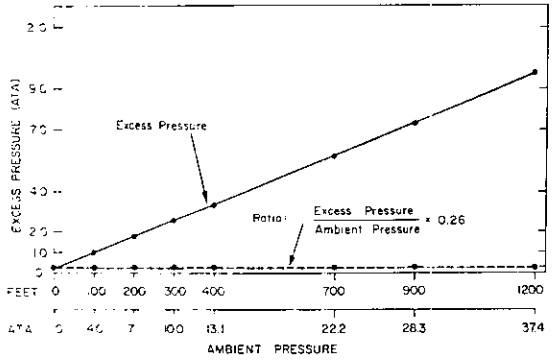

FIG. 8. Predicted isobaric inert gas counterdiffusion supersaturation at an oil-water interface (N_2 diffuses through the oil side, He diffuses through the water side). Using the values for solubility and diffusion characteristics for N_2 and He summarized in Table 3, maximum theoretical degrees of isobaric "counterdiffusion supersaturation" have been calculated. Figure indicates that, with a constant ratio of supersaturation pressure to ambient pressure of about 0.26, massive degrees of supersaturation are predicted, even without change in ambient pressure (isobaric state). At 37.4 ATA pressure of our human studies, theoretical supersaturation at some points may have reached nearly 10 ATA.

Trial of the concept of isobaric bubble formation in physical systems involving helium-nitrogen counterdiffusion across oil-water layers demonstrated that formation of visible gas bubbles occurs at the oil-water interface (12). The occurrence of growth of a gas phase during a form of isobaric counterdiffusion in physical systems has recently been further examined. The observations on isobaric gas phase growth in gelatin by Strauss and Kunkle (30), which were begun by Strauss in this laboratory following our observations and explorations of the mechanism of gas lesion development in isobaric gas counterdiffusion, indicate that helium diffusion into bubbles in gelatin initially exceeds the rate of nitrogen loss, leading to growth of bubbles of visible size.

Demonstration of Gas "Bubble" Formation in Living Systems

The concept that the dermal lesions observed in man contained accumulations of gas was still further validated by exposure of pigs to the same counterdiffusion process at pressures to 10 ATA (16, 21). In no instance were cutaneous

TABLE 3. *Gas constants used in computing excess gas pressure development during isobaric counterdiffusion, in Fig. 8*

Gas	Solubility						Diffusion Coefficient						Permeability*	
	Oil			Water			Oil			Water			Oil	Water
	Bunsen coef, cm³/ml per ATA	Temp, °C	Ref	Coef, cm³/ml per ATA	Temp, °C	Ref	Diffusivity, cm²/s	Temp, °C	Ref	Diffusivity, cm²/s	Temp, °C	Ref	Permeability, cm²/s per ATA	Permeability, cm²/s per ATA
Nitrogen	0.067	37	7	0.01270	37.05	9	0.704×10^{-5}	37	28	3.01×10^{-5}	37	28	0.047×10^{-5}	0.0382×10^{-5}
Neon	0.01930	37.6	17	0.0096	37.0	23	(0.834×10^{-5})†	37	28	(3.48×10^{-5})†	37	28	0.0161×10^{-5}	0.033×10^{-5}
Helium	0.0148	38	2	0.0084	37	23	(1.86×10^{-5})†	37	28	(7.92×10^{-5})†	37	28	0.0275×10^{-5}	0.067×10^{-5}

Oil-water thickness ratio 0.72. * Product of Bunsen solubility coefficient and diffusivity (11). † Numbers in parentheses computed from N_2 values and Graham's law (28).

lesions seen when the animal breathed helium and was surrounded by nitrogen or neon. With respiration of nitrogen-oxygen or neon-oxygen mixtures while exposed to helium, cutaneous gas lesions formed at the 10, 7, and 4 ATA ambient pressures employed. With nitrous oxide breathing in a helium environment severe dermal gas lesion development occurred even at 1 ATA, with subcutaneous gas accumulation and even grossly visible venous and arterial gas embolization, leading to death of the counterdiffused animal through massive circulatory obstruction (16, 21). At death, secondary gas lesions are found in all organs and tissues, due to gas bubbles delivered via the arterial blood (21).

Dynamics and Forms of Isobaric Gas Counterdiffusion

Superficial tissue counterdiffusion. Our published analysis of the counterdiffusion process (11, 12) has described stable-state relationships in a simple two-layer system. In man and the experimental animal the composition of tissue must be expected to be more complex, with probably many millions of minute interfaces of many different physical-chemical characteristics. Thus, the rates of onset, rates of gas phase growth, and the consequences of bubble formation will vary, not only with the gases themselves and their pressure gradients but with multiple features within an involved tissue. At this point in time it is not known exactly where and by what mechanism (by bubble formation or growth of preexisting nuclei) gas phase evolution in the skin occurs. Nor is it yet known whether gas bubbles actually form within the capillaries of skin to initiate the ultimate embolic phase of the process or enter from sites of formation in surrounding tissue spaces. Either or both together should be considered possible. The rate of development of symptoms and lesions and the rate of physiological deterioration due to continuous embolization will depend on the gases employed, the pressure, and, to an as yet unknown degree, the temperature and circulatory perfusion of the tissues involved.

Deep tissue counterdiffusion. The concepts elaborated above require counterdiffusion between a gas phase (e.g., ambient atmosphere) and underlying tissue capillaries. As such the process could involve counterdiffusion between blood and gas-containing spaces within the body (paranasal sinuses, alveoli, bowel, middle ear (22)) although this is less clearly established at present than the process involving the ambient gas space.

No indication as yet exists that deep tissues served by arterial blood, but not in contact with a true gas space, are sources of gas bubbles in counterdiffusion exposures. However, a second deep tissue form of "isobaric inert gas exchange" does occur in such deep tissues and can lead to supersaturation or desaturation of the deep tissues when the composition of a respiratory gas mixture is altered. An example of this highly important second form of isobaric inert gas counterdiffusion is illustrated in Fig. 9. In an individual exposed to an increased ambient and inert gas pressure, such as air breathing at an undersea depth of 200 ft of seawater, all body tissues will be exposed to a progressively increased nitrogen pressure, toward equilibrium with the inspired nitrogen partial pressure. At any point in time, if helium is abruptly substituted for nitrogen in the

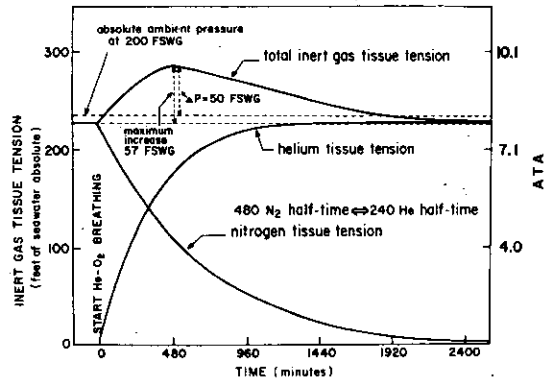

FIG. 9. Deep tissue form of isobaric inert gas counterdiffusion. Diagrammatic representation of time courses of changes in He, N_2, and sum of He + N_2 pressures in a hypothetical tissue or cellular fluid. Tissue selected has a half-time for N_2 elimination of 480 min, compared with 240 min for He uptake. At an unchanged ambient pressure (isobaric state) equivalent to a depth of 200 ft of seawater, abrupt change from N_2 to He breathing (with natural P_{O_2}) leads to more rapid uptake of He than elimination of N_2. The result is a transient inert gas supersaturation (sum of P_{He} + P_{N_2} exceeds ambient pressure) which may be several atmospheres in magnitude.

respired gas, the arterial blood delivered to all tissues will, within the time course of pulmonary washout, contain helium at a partial pressure close to that inspired. The inert gas gradients established between the tissue and capillary will then induce a theoretically recognized form of deep counterdiffusion in which nitrogen leaves the tissue while helium enters. What is not generally appreciated is that, as this process proceeds with no change in ambient pressure (under isobaric conditions), the *entry of helium* into certain tissues is more rapid than the *exit of nitrogen* from them, leading to the second (deep tissue) form of isobaric inert gas supersaturation. This "deep tissue" form is transient, not sustained and progressive as is the case with the form described for superficial tissues in contact with the ambient atmosphere. The study of bubble growth in gelatin exposed to helium (30) relates to this deep form of isobaric gas counterdiffusion which was a recognized component of the respiratory studies in which gas lesions developed (19). Such *supersaturation* should not be considered as occurring uniformly in tissues but must vary in time course and degree in many and widespread minute locations having different rates of perfusion by blood and different histochemical composition. The opposite effect, accelerated *desaturation*, is accomplished by substituting the breathing of nitrogen or another relatively slowly saturating gas for helium or another gas which saturates tissues rapidly.

The "deep tissue form of isobaric counterdiffusion supersaturation" is cited here to *a*) provide a distinguishing designation for it and *b*) point out that it represents a mechanism of distinct hazard whereby either primary generation of deep bubbles or accelerated growth of preexisting bubbles can be induced (even as in superficial isobaric gas counterdiffusion lesions and subsequent embolism, or in any lesion of decompression sickness related to diving, tunneling, or aerospace activities).

In the experiments described here, it is considered that the suggested deep tissue counterdiffusion process also occurred, superimposed upon the results of the surface form, increasing the size of bubbles generated by the surface form of counterdiffusion. Such an event would be expected on return to helium breathing following a period of exposure to nitrogen or neon breathing.

Specific Targets of Isobaric Gas Counterdiffusion in Man and Animals

Two structures other than skin are here identified on anatomical bases as potential sites for development of superficial isobaric gas counterdiffusion lesions, namely the ear and the eye. In each of these structures it is conceived that large counterdiffusion gradients of inert gases existed in the human subjects who developed symptoms of dermal or vestibular involvement. The details of gas exchange conceived as occurring in eye and ear are beyond this present description of the bases for the overall counterdiffusion syndrome as observed in man. The extensive observations and analysis of vestibular changes are presented separately (22) and indicate the possibility that the isobaric inert gas counterdiffusion process may have occurred through the round window, between the middle ear and inner ear, with localized bubble formation in inner ear fluid.

While direct intraophthalmological inspection of the human subjects was not performed during counterdiffusion in the pressure chamber, there is no indication that bubble formation occurred in either the eye or conjunctivae of the subjects in any of their multiple exposures.

Considering the concept and the implications of bubble formation in eye and inner ear, detailed investigation of the relationship of counterdiffusion gas exchange to both the eye and the entire ear mechanism is certainly necessary.

Implications of Gas Counterdiffusion in Respiratory Function and Environmental Sciences

The relationships to undersea activity of counterdiffusion gas lesion development, embolism, and vestibular dysfunction are clear. Use of respiration of the slower saturating gases such as argon, nitrogen, and neon to speed elimination of helium during decompression from high helium pressures can probably be considered practical when the body (including the head and ear canals) is surrounded by the gas breathed. However, it is critical to assume until proven otherwise that use of a mask which leaves ear canals, eyes, and skin exposed to a gas which diffuses more rapidly than the respired gas provides the condition for development of damaging gas lesions or gas embolism.

It is further important to consider that superimposition of decompression upon isobaric gas lesion development, and vice versa, presents the likelihood of gross expansion of bubble size by decrease in ambient pressure. Decompression problems should also be magnified as gas bubbles generated by the superficial form of gas counterdiffusion are caused to grow on reaching deep tissues or central venous blood already oversaturated with inert gases.

The phenomenon of continuous gas lesion development and embolization provides an important laboratory method for study of the effects of embolization, the interactions of bubble surfaces and blood, and for therapy of gas lesion diseases.

The rapid occurrence of fatal gas embolization in animals during nitrous oxide-helium counterdiffusion at 1 ATA makes it necessary to examine circumstances of clinical anesthesia for evidence of gas lesion development. In clinical procedures requiring concurrent use of membrane oxygenators and anesthesia, analysis of the counterdiffusion process indicates that bubble formation or growth may occur (26), and bubble growth has been observed in such devices.

It is expected that as investigations of the fundamental processes involved in isobaric gas counterdiffusion proceed still other implications for biology, physics, and medicine will evolve.

These unexpected observations and their initial evaluation in man were made during the course of a planned study concerned with respiratory, pulmonary, and neurophysiological effects of gases, involving several investigative groups (19). Particular contributions to the analysis of the isobaric counterdiffusion phenomena were made by Thomas Liebermann, a subject, who performed the direct dissection of a cutaneous gas lesion at increased ambient pressure (37 ATA); Mrs. B. Hanley, who assisted in construction of the protective "expired gas suits"; Mr. R. Gelfand, Drs. R. Peterson, R. Strauss, and B. Wright, who participated in the respiratory studies which led to the development of the gas lesion phenomena; and Dr. J. G. Dickson, who supervised environmental chamber safety. Drs. D. Graves and J. Quinn directly collaborated in evaluating the theoretical bases for the concept of isobaric gas supersaturation.

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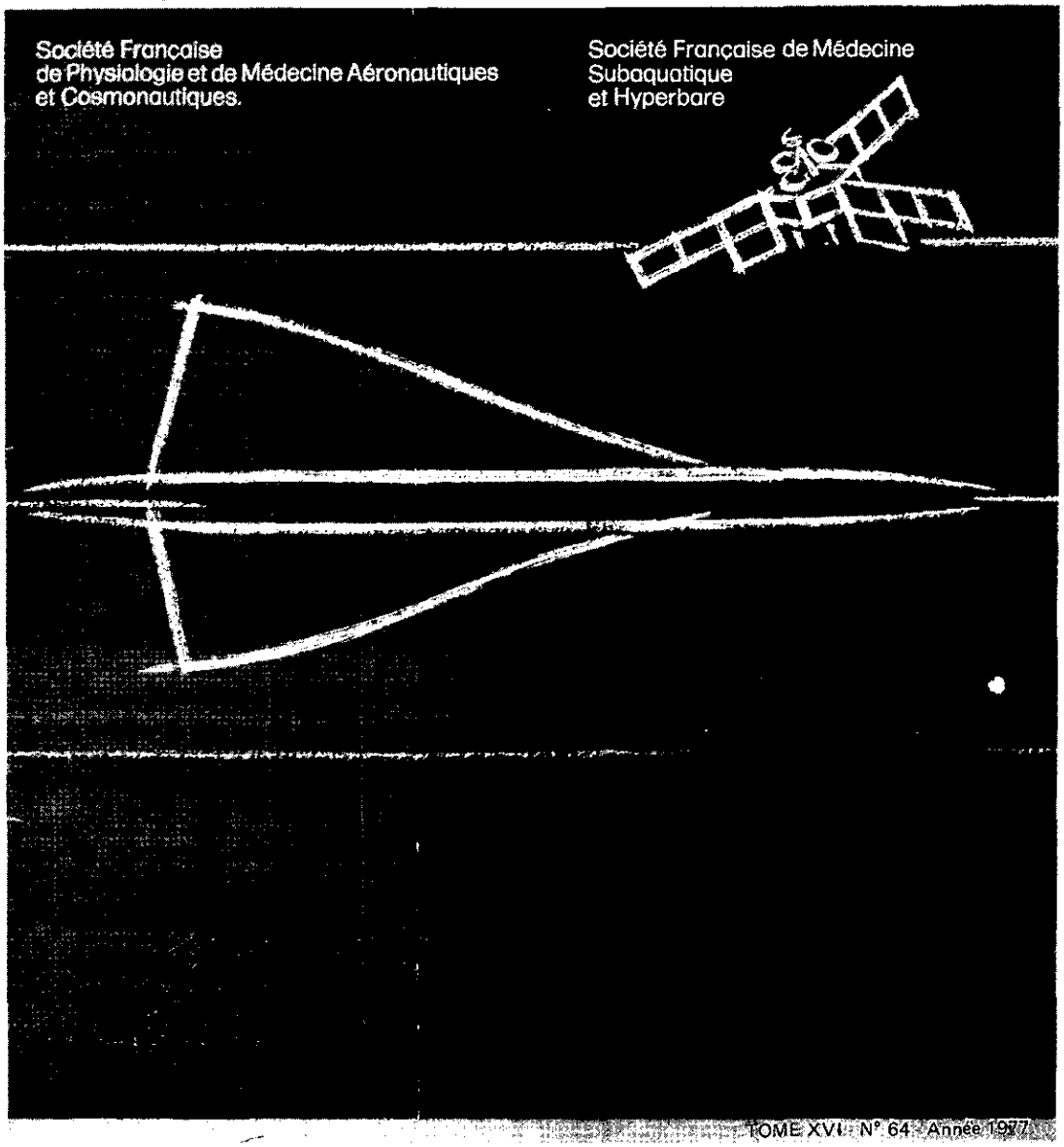
médecine aéronautique et spatiale

médecine subaquatique et hyperbare



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18. Vestibulocochlear dysfunction in squirrel monkeys in simulated diving experiments

by J.P. LANDOLT*, K.E. MONEY, E.D.L. TOPLIFF, K.D. POWERS and W.H. JOHNSON**

INTRODUCTION

With increasing frequency, vestibular and cochlear disorders are being recognized as potentially serious sequelae of compressed air (e.g., caisson sickness) and diving experiences. Particularly pertinent are the otologic incidents resulting from decompression sickness. For instance, Bühlman and Waldvogel (1) report a 13 % incidence of vestibulocohlear symptoms in experiments designed to treat decompression sickness. Kennedy (2) asserts that these incidents may be even higher within the civilian population involved in diving and compressed air work. Significantly, the manifestations and symptoms of inner ear decompression sickness are quite specific. The sickness appears quite suddenly, during or shortly after decompression, with one or more of the following symptoms : vertigo, nystagmus, nausea, emesis, hearing loss, tinnitus, and loss of spatial orientation (1, 3-6). Significant also is the fact that recompression therapy is often beneficial and that the vertigo gradually disappears over a period of up to three weeks (3-4).

To date, only a few studies have used animals to investigate vestibulocochlear dysfunction resulting from compressed air environments. Of significance is the early work of Alt, Heller, Mager and Von Schrotter (7), who reported hemorrhagic incidents in the fluid spaces of the inner ear in animals subjected to rapid decompression. Recently, McCormick and his colleagues (8, 9) reported loss of cochlear potential, bubble formation and hemorrhage in the inner ear, and the appearance of a proteinaceous exudate in the perilymphatic spaces of the cochlea in guinea pigs that were subjected to decompression. In this communication, the nature and extent of vestibulocochlear dysfunction is described in squirrel monkeys (**Saimiri sciureus**) that have undergone rapid decompression in simulated diving experiments.

* Defence and Civil Institute of Environmental Medicine
1133 Sheppard Avenue West, P.O. Box 2000
Downsview, Ontario - Canada M3M 3B9

** Department of Otolaryngology - University of Toronto
Toronto, Ontario - Canada

MATERIALS AND METHODS

Diving experiments were performed in a 300 m hyperbaric chamber (Bethlehem Corp., 0.173 m^3 capacity). Before the dive, a myringotomy was performed under light Nembutal anesthesia in both ears to prevent otic barotrauma in the monkeys. Electronystagmography (for both horizontal and vertical eye-movements) was used to record pre-dive and post-dive spontaneous, positional, and post-rotatory nystagmus. Any monkey showing pre-existing signs of spontaneous or positional nystagmus was considered unfit for the diving experiments. Monkeys were sacrificed under very deep Nembutal anesthesia ($\simeq$ 1 ml/kg mass) with intracardiac (10 % formalin) perfusion. Temporal bones were decalcified, embedded in celloidin, horizontally sectionned at 20 μm and stained with hematoxylin and eosin (10). Brain sections of the cerebral cortex, cerebellum, and brain stem were also prepared by the celloidin method.

Vestibular dysfunction was determined by correlating histopathological with nystagmographic and behavioural observations. Cochlear pathology was determined solely from histological observations.

The diving profile that has been most useful in producing discrete inner ear dysfunction is one that starts with an oxygen - helium gas mixture (20:80) from the surface to 13.9 meters of sea water (msw). Compression in then via helium at the rate of 32.6 msw per minute to a depth of 274 msw, while maintaining the oxygen partial pressure at 50.7 Pa. Decompression after one minute bottom time is at the rate of 18.3 msw per minute to 61 msw ; and then in steps of 6 msw every 4 minutes to surface. Signs of decompression illness in monkeys were remedied by recompressing to twice the depth at which the illness occured, and the monkey was then brought to the surface at the rate of 0.3 msw per minute.

RESULTS

The results reported herein are based on the behavioural observations of vestibular dysfunction, electro-

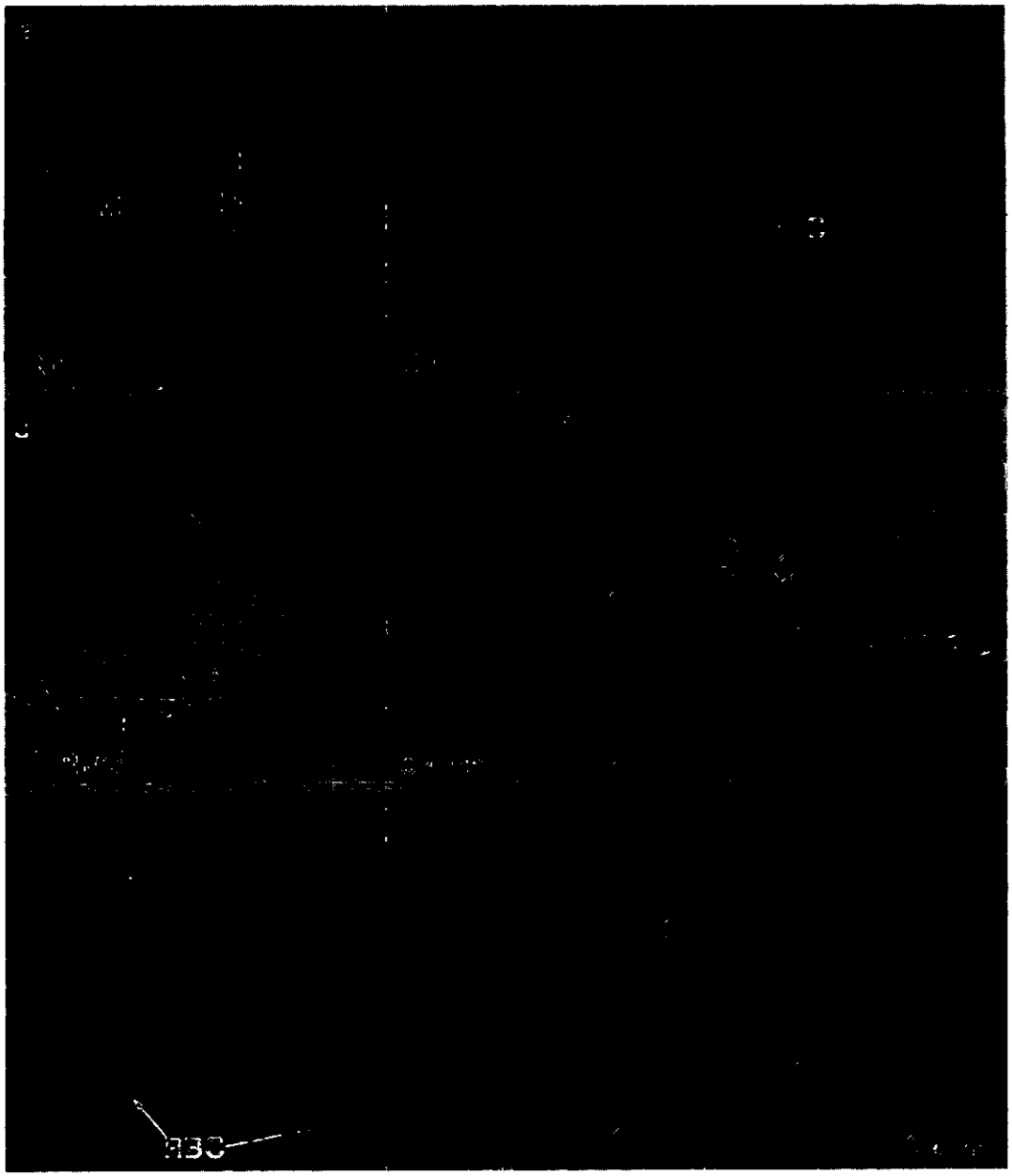

Figure 1 : Histopathology in vestibular apparatus resulting from decompression. *(a)* Part of vestibular apparatus in a normal monkey illustrating macula utriculi, MU, crista ampullaris, CR, with cupula, CU, of lateral semicircular canal and their innervation, NF. E and P designate endolymphatic and purilymphatic spaces, respectively. *(b)* Monkey 2 ; 7 days survival post-dive. Illustrating precipitous material, PR, in anterior semicircular duct (in E) and hemorrhage, RBC, in associated semicircular canal (in P). *(c)* Monkey 20 ; 6 days survival post-dive. Illustrates PR (arrows) in E. Note red blood cells, RBC, close to innervation of MU. *(d)* Monkey 40 : 2 1/2 hours survival-dive. Arrows outline PR adhering to CU. *(e)* Illustrates PR (arrows) in E and on CU, and RBC near innervation to CR of anterior semi-circular canal in Monkey 20. *(f)* Monkey 4 ; 7 days survival post-dive. RBC in P around ampulla of CR of posterior semicircular canal. Note normal CU.

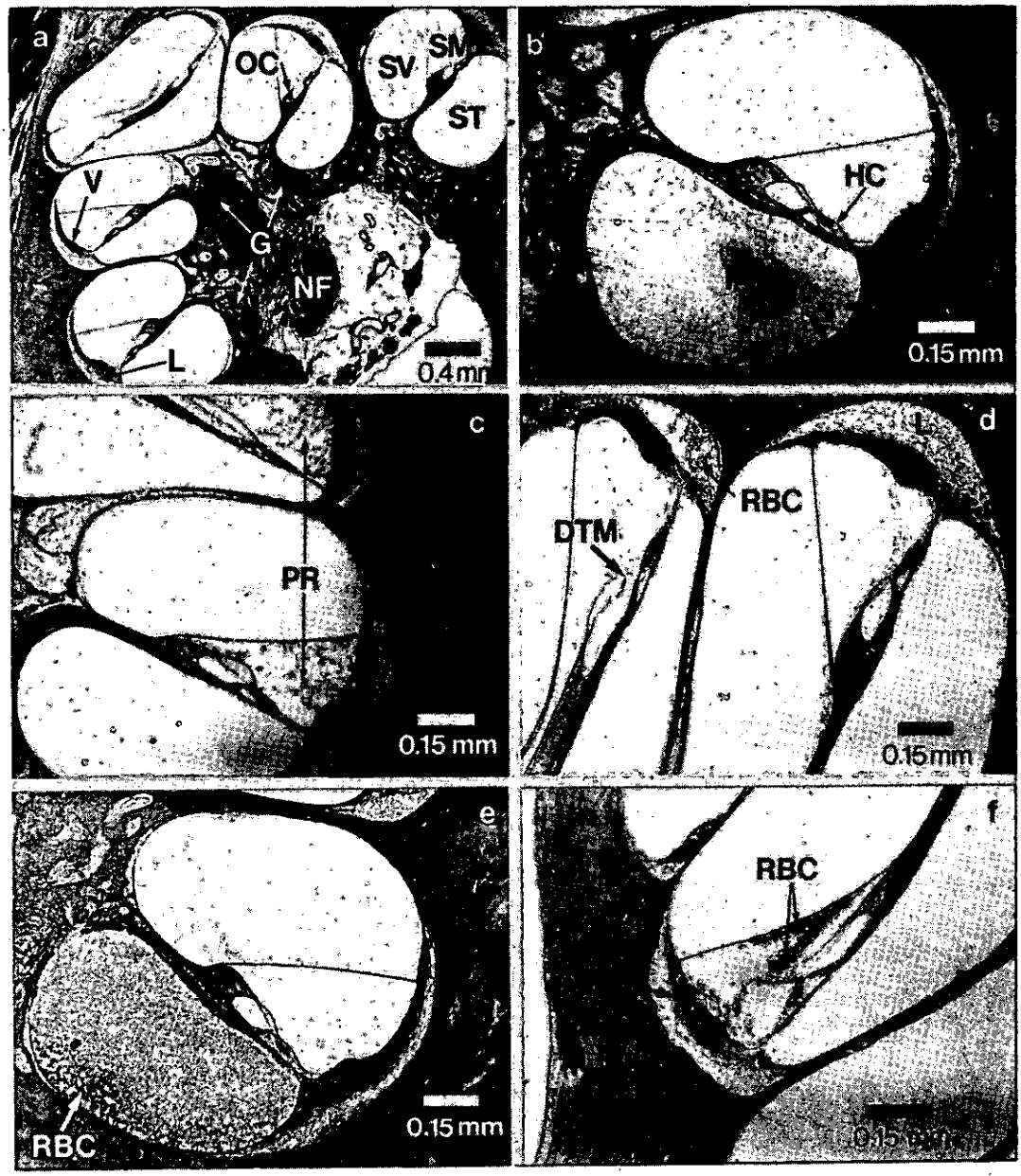

Figure 2 : Histopathology in cochlea resulting from decompression. *(a)* Normal cochlea illustrating the scala vestibuli, SV, the scala tympani, ST, the scala media, SM, the sensory organ of Corti, OC, the stria vascularis, V, the spiral ligament, L, the spiral ganglion cells, G, and their fibers, NF. *(b)* Monkey 7 ; 1 1/2 hours survival post-dive. Illustrating precipitous material, PR, in SV of basal turn in cochlea. HC represents intact hair cells. *(c)* Monkey 19 ; 3 1/2 hours survival post-dive. Illustrating PR in SM of middle and apical turns in cochlea. *(d)* Monkey 12 ; 2 days survival post-dive. Illustrating damage to L, which is detached from wall with resulting space filled with red blood cells, RBC. Note the detached tectorial membrane, DTM, of OC. Traces of PR are shown in SM in both turns of the cochlea. *(e)* Monkey X ; 8 days survival post-dive. Hemorrhage, RBC, in ST resulting from damage to collecting venules. *(f)* Monkey 10 ; 1 1/2 hours survival post-dive. RBC result from damage to V.

nystagmographic tests, and histology in 22 monkeys *in which recompression therapy was not effective in* abolishing signs of the vestibular «hit». Behaviourally, a vestibular hit was identified in the majority of monkeys by the sudden onset of a head nystagmus during the decompression phase of the dive. Other behavioural *manifestations of vestibular dysfunction resulting from* the dive include emesis, head tilt in one direction, and unsteadiness («staggers»). The decompression schedule caused discrete inner ear damage in approximately 35 % of the monkeys exposed.

The membranous inner ear is comprised of a series of interconnected ducts and sacs which contain the sensory epithelia of the vestibular apparatus and the cochlea, for equilibratory and auditory functions, respectively. *The major sensory epithelia* of the vestibular apparatus are the statoconia-covered maculae utriculi (figure 1a) and sacculi and the cupulae covered cristae ampullares of the anterior, lateral (figure 1a), and posterior semicircular ducts. The sensory epithelium for the *perception of sound, in the mammal*, is in the organ of Corti, which spirals the lenght of the cochlea (figure 2a) within the scala media. The sensory regions are all bathed in sodium ions. In the cochlea, the two remaining spaces — the scala vestibuli and scala tympani (figure 2a) — con*tain perilymph (a fluid rich in sodium and low in potas*sium), as do the remaining spaces in the inner ear. Specialized networks of vessels supply and drain the different parts of the inner ear (11, 12).

The most striking histological observation in all monkeys that received a vestibular hit was the appearance of an amorphous precipitate in the fluid spaces of the inner ear. In the cochlea, it was found in all scalae (e.g., see Figs. 2b and 2c), and in some cases on the tectorial *membrane* of the organ of Corti (fig. 2c). In the vestibular apparatus, it was occasionally found in the perilymphatic spaces but always in the endolymphatic spaces (figs. 1b and 1c). Frequently, this precipitous material appears as an agglutinate adhering to the gelatinous cupulae of the cristae ampullares (figs. 1d and 1e). Electronystagmographic tests show the presence of strong positional nystagmuses in these monkeys (fig. 3a). The suggests that the cristae ampullares, which normally act as sensors of angular acceleration, now also respond to gravity as a result of this adherent material. The post-rotatory tests further indicate a reduced sensitivity of the end organ to rotatory stimulation (fig. 3b). The same precipitous material was often seen on the macula of the utriculus (fig. 1d), but seldom of the sacula of the sassulus.

In the vestibular apparatus, hemorrhagic sites were confined to the perilymphatic spaces (figs. 1c, 1e and 1f), often in the regions where nerve fibers enter the cristae ampullares and/or the maculae utriculi (figs. 1c and 1e). Sometimes blood pooling was observed in the perilymphatic space alongside the semicircular duct (fig. 1b). When this occured, it appeared as if there was a tearing of connective tissue and blood vessels (with consequent hemorrhage) from the periosteum of the bony semicircular canal. Only occasional red blood cells were found in the endolymph of the vestibular apparatus. In the cochlea, tissue damage and hemorrhage do not

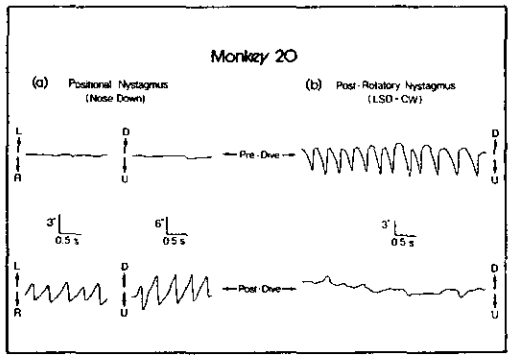

Figure 3 : Comparison of electronystagmograms prior to and at 3 days following a dive in which there was vestibular dysfunction resulting from rapid decompression in Monkey 20 (c.f. Figs. 1c and 1e). Left-right (L - R) directions refer to horizontal eye-movement tracings ; down-up (D - U) directions *to vertical eye-movement tracings. (a)* Lower tracings illustrate the significant positional nystagmuses (both horizontal and vertical) that occured as a result of the dive. (Upper tracings are normal). *(b)* Lower tracing illustrates abnormal post-rotatory nystagmus to clockwise (CW) rotation with head left side down (LSD). (Upper tracing is normal).

appear to be confined to a specific scalae. They have been observed in the basal, middle and apical turns in all scalae. Tissue damage, when it occurs, does so in the region of the spiral ligament (fig. 2d), the contiguous blood vessels in the membranous wall (in particular, in the collecting venules which pass over the scala tympani — see fig. 2e), and the stria vascularis (fig. 2f).

Interestingly, there does not appear to be gross tissue damage, either to the hair cells of the vestibular apparatus (figs. 1e to 1f) nor to those of the organ of Corti (figs. 2b to 2f). Furthermore, brain lesions have been found in the monkeys judged to have suffered a discrete inner ear hit.

DISCUSSION

The view that inner ear decompression illness results from gas emboli in the labyrinthine vascular system is strongly supported by the results reported herein. In the first place, the sudden appearance of the vestibular hit suggests a rapid disruption of labyrinthine structures such as would be encountered in bubble formation and growth in situ with consequent blood vessel blockage and/or rupture and hemorrhage. With prolonged blockage, it is likely that the blood vessels (probably the post-capillary segments and the venules) would be deprived of oxygen and the consequent endothelial cell changes would lead to an increased vascular permeability with concomitant exudation of blood *proteins* into the extravascular spaces. This exudate then appears in the scalae of the cochlea, as reported by McCormick and his colleages (8, 9), and it also appears in the semicircular ducts, the macula utriculi and, in particular, on *the cupulae of the cristae ampullares. Given the fact* that hemorrhage and/or the appearance of a precipitous material in the inner ear have been found in these mon-

keys, it is not surprising that recompression therapy often fails to reverse the effects of vestibular hits. It would appear likely that only when there are gas bubbles in the endolymph and/or the perilymph, can recompression therapy the beneficial or when intravascular bubbles are insufficient to cause irreversible damage.

Aside from bubble formation, one cannot overlook the fact that other causative factors may also be important in inner ear decompression sickness. In this regard, Philp (13) cites evidence that a hypercoaguable state may occur as a result of a blood-bubble interface reaction. Interestingly, McCormick and his colleages (8) observed a decrease in cochlear microphonic potential loss in decompressed guinea pigs that had been treated intravenously with heparin before the dive compared with the potential change in those not so treated. This suggests that heparin, an anticoagulant, may conceivably prevent lipid, embolic, and hypercoagulation phenomena from occuring in the microcirculature of the inner ear. Confirmation of this hypothesis awaits further studies.

ACKNOWLEDGEMENTS

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SPECIAL ARTICLES—Continued.

CLINICAL NOTES:

AUDITORY ACUITY IN SUBMARINE PERSONNEL

By Lieutenant Commander Charles W. Shilling, Medical Corps, United States Navy, and Chief Pharmacist's Mate Ira A. Everley, United States Navy

Part III

Rapid change in atmospheric pressure is often manifested by an inflammatory reaction in the middle ear, which, in turn, may lead to acute or permanent loss of auditory acuity. We have completed a study on each of these conditions, and because of their interrelationship, present them as section A and section B of part III of the series on *Auditory Acuity in Submarine Personnel.* Section A is a study of "Aero-otitis Media in Submarine Escape Training" and section B is "Hearing Loss Due to Exposure to Increased Air Pressure."

SECTION A

AERO-OTITIS MEDIA IN SUBMARINE ESCAPE TRAINING [1]

At the Submarine Escape Training Tank, United States Submarine Base, New London, Conn., every candidate for "lung" training is sub-

[1] We wish to express our appreciation to Lt. Shirley H. Baron (MC), USNR, for his counsel and aid in interpreting the damage to the ears.

jected to 50 pounds increased air pressure in the recompression chamber, as required by training regulations, prior to entering the water for actual training with the submarine escape appliance.

As the air pressure in the chamber is raised, a feeling of fullness on the ear drums is noted because of the inequality in pressure on the two sides of the drum caused by restricted air flow through the eustachian tube to the inner side of the drum in contrast to the more ready flow through the external auditory canal to the outer side of the drum.

The eustachian tube acts as a ventilating shaft and as a means of drainage for the middle ear. In the resting state its walls lie in apposition, but notwithstanding this, for the majority of those taking air pressure, it permits sufficiently rapid equalization so that no real difficulty is experienced. If any difficulty is experienced, the act of swallowing or yawning causes the dilator muscles to contract and thus the tube is opened which for many is all the additional help necessary to facilitate equalization of air pressure. Others find that by closing the mouth, holding the nose and "blowing against the ears" they can more readily facilitate the opening of the eustachian tubes and thus achieve the rapid equalization necessary in taking high-pressure air. An ear which is temporarily "blocked" may suddenly give way with a high pitched squeak which is audible to all those near the subject.

However, in some cases, none of these acts are effective in permitting equalization of pressure and if the application of air pressure is continued under these conditions, aero-otitis media results and it is with this condition that this paper is concerned.

Failure to properly ventilate the middle ear may be the result of ignorance or inexperience, but equalization or ventilation may be temporarily impossible according to Armstrong and Heim (1) because of any of the following conditions: "Stenosis of the eustachian tube as the result of acute and chronic infections of the upper part of the respiratory tract, nasal obstruction, sinusitis, tonsillitis, tumors of the nose and nasopharynx, paralysis of the soft palate or superior pharyngeal muscles, enlargement of the pharyngeal or tubal tonsil, inflammatory conditions of the eustachian tube or middle ear and scar tissue about the ostium of the eustachian tube." If such conditions exist the air pressure increase must be stopped and the subject returned to atmospheric air pressure (locked out) or there will be sharp pain in the ears accompanied by damage to the drum and middle ear.

This damage Armstrong and Heim (1) have called aero-otitis media

> * * * an acute or chronic traumatic inflammation of the middle ear caused by a pressure difference between the air in the tympanic cavity and that of the surrounding atmosphere, commonly occuring during changes of altitude

in airplane flights and characterized by inflammation, discomfort, pain, tinnitus, and deafness.

Lovelace, Mayo, and Boothby (2) say:

Aero-otitis media is caused by the lack of ventilation of the middle ear during changes in atmospheric pressure to such an extent that traumatization occurs in the tympanic cavity.

At this point it might be well to note that whereas the pressure difference between atmospheric pressure (760 mm. Hg.) and 18,000 feet (380 mm. Hg.) is only 380 mm. of mercury, the difference between atmospheric pressure and 50 pounds (gage) increased air pressure is 2,585 mm. of mercury.

In our experience, the damage which can be noted with the otoscope ranges all the way from very slight congestion through marked congestion or inflammation, retraction, bleb formation caused by actual hemorrhrage into the drum membrane, to complete rupture of the drum with frank hemorrhage from both the external canal and the eustachian tube. To the uninitiated, it is truly alarming to look at an ear that a few minutes before was white, glistening and normal and see a fiery red drum so congested and retracted as to cause obliteration of all normal landmarks and covered with bubble-like bulges caused either by air or hemorrhage disecting the strata of the drum membrane. Often this active congestion and hemorrhage extends onto the walls of the external auditory canal and must also extend into the tympanic cavity for blood at times comes from the eustachian tube in the absence of a rupture of the drum membrane.

Manigan (3) found "a fully retracted drum", "ecchymotic hemorrhages into the drum" and "inflammation around the pharyngeal opening of the eustachian tube." He also reports, "hemorrhagic blebs in the external aural canal or on the drum membrane as the result of air trapped in the middle ear."

The individual complaints vary with the degree of damage from a mild feeling of fullness or "water in the ears" to excruciating pain. Deafness, either partial or complete, is an almost constant complaint. Tinnitus is a frequent complaint.

Some subjects experience severe pain in their sinuses, usually the frontal. This pain may be noted first when the pressure is being built up. It may be lancelike and momentary, but frequently is steady and severe enough to necessitate the pressure being stopped and the subject "locked out" to normal air pressure again.

Nosebleed is occasionally encountered probably because of excessive trauma when holding the nose and "blowing against the ears." Bleeding, of course, occasionally comes from sinuses. Cases of severe toothache have at times developed under pressure which were relieved

upon return to atmospheric pressure. Hidden cavities and leaky fillings have been invariably found in these cases.

A few case histories may serve to illustrate more clearly the various types of damage encountered in attempting to take 50 pounds increased air pressure.

CASE REPORTS

Patient T.—January 13, 1941. Complained of pain in both ears, which was of such severity that air pressure increase was halted at 7 pounds and the subject put in the outer lock where the air pressure was slowly dropped to normal atmospheric pressure while the others in the main compartment continued to increase the pressure until reaching 50 pounds. Examination revealed moderate congestion of both drums. By next morning there was evidence of clearing of the condition and by the 16th of January he was considered to be ready to try it again.

Patient N.—December 23, 1940. Unable to take more than 20 pounds pressure so was "locked out" as described above. Complained of pain in the left ear only. Examination revealed right ear normal but left with marked congestion, retraction and bubblelike areas of hemorrhage into the drum membrane. Spit out considerable blood-streaked material draining from left eustachian tube. December 24.—Some lessening of congestion. December 26: clearing nicely with areas of hemorrhage becoming deep purple. December 27: clearing continues with areas of hemorrhage showing organization with change to orange brown color. January 22, 1941: left drum completely cleared of acute condition but dull, thickened and showing areas resembling scars.

Patient Ni.—January 6, 1941. "Locked out" of pressure at 12 pounds. Complained of pain in the region of the frontal and ethmoidal sinuses. The frontal sinuses were cloudy to translumination and by x-ray also showed involvement. January 7: Pain continues despite local heat and shrinkage of nasal mucous membrane. January 8: As pain continues patient turned in sick bay for continuous treatment. January 13: Discharged to duty, free from pain.

Patient C.—January 2, 1941. At the original ear examination both drums were dull, scarred and retracted, and the left had a large white plaque around the periphery and also a very thin translucent area just off center at about 4:30 o'clock. He was advised of the condition but since he was an officer candidate for Submarine School who had been sent a long distance, he was allowed to attempt "lung training". While taking pressure, he noted pain in his left ear and then a feeling as if something had given away followed by relief of pain. He completed his training and reported to the Submarine Medical Examiner. A large perforation with ragged edges was found to have completely replaced the thin area noted prior to taking pressure. The ear remained clean and dry and the drum healed over by the 18th of January but the area of the scar is so large and thin that it will undoubtedly rupture again at the least pressure.

Patient D.—November 8, 1940. Took 50 pounds pressure without any difficulty but as the pressure was being dropped felt slight pain and there suddenly appeared a marked hemorrhage of the left ear and of the nose. Contrary to instructions this man "held his nose and blew" while pressure was being dropped, thus inhibiting equalization of pressure. Examination of left ear after cessation of hemorrhage and cleaning out of canal revealed a drum which was a deep purplish-red with a rupture of fair size on the periphery of the drum at 11:30 o'clock (pars flaccida), with blood still dripping from the perforation. Examination of the right ear showed marked congestion, bulging and evidence

of hemorrhage into the drum membrane but no rupture. Because of the danger of infection, the man was turned in on the ward where the ward medical officer wanted to lance the right ear, refusing to believe that it had been normal upon examination less than an hour before. November 30: The right ear has cleared except for an area of organizing hemorrhage now brownish purple in color. The left ear drum however, is purplish-black in its entirety and devoid of the normal landmarks although the ruptured area has healed over. December 3: Both ears are almost normal except that the drums are dull and thickened and a brownish area still persists in the right ear.

Patient M.—January 8, 1941. Completed the pressure and the "lung" training but had continual pain in left ear since that time until reporting to sick bay on January 11 at which time there was marked bulging of drum with evidence of acute inflammation. Was given local treatment and general sedation but on January 12 condition was worse and a paracentesis was done with a heavy drainage of pus and marked relief of pain. Ear drained for a few days but eventually healed without complication. Although a mild upper respiratory infection was present at the time of admission on the 11th of January, it is believed that the otitis-media had its origin in the air pressure experience on the 8th as the pain had continued from that time.

Patient L.—Developed acute mastoiditis requiring immediate hospitalization. This developed almost immediately following a painful pressure exposure and there can be no doubt as to the etiology.

It is worthy of note that during the fiscal year July 1, 1940, to June 30, 1941, in which this study was undertaken, there were 4,333 officers and men examined for "lung" training. Of this number there were 256 turned down from the following defects: Catarrhal condition of upper respiratory tract, 109; otitis externa, 48; tachycardia, 35; hypertension, 38; other general causes, 24. There were an additional 222 who failed to equalize pressure and were thus, at least temporarily, prevented from completing training. These conditions were in the main, only temporary for there were but 19 who were permanently disqualified and taken off submarines; 9 because of failure to equalize pressure; and 10 because of defects, noted during the physical examination, of a nature serious enough to necessitate disqualification.

Two thousand seven hundred and fifty-one of the men taking the 50-pound pressure test were included in this study. Of these, 1,866 were taking pressure for the first time, 44 had tried before but never successfully completed the pressure test, and 941 had the pressure 1 or more times previously. Of the men taking pressure for the first time there were 152 men having ear trouble of sufficient severity to cause them to be "locked out" of the chamber before completing the test. This usually occurred before reaching 10 pounds. In addition, there were 139 men who had enough trouble to require the increase of air pressure to be stopped 1 or more times during the test. Of the experienced men taking pressure, there were 55 "locked out" and 25 who had to stop in order to equalize. Sinus pain forced a total of

9 men to come out of the tank while, in addition, there were 26 who experienced pain while the air pressure was increasing, and 9 who experienced it during the dropping of the pressure. There were 40 men who experienced nosebleed during or immediately following the pressure test.

The clinical entity termed "areo-otitis media" is new only in its application to aviation medicine since traumatic pressure injury to the middle ear was observed and described as early as 1896 when Alt (4) reported three cases of "apoplectiform labyrinthitis" in caisson workers. However, his cases may have been due to compressed-air illness for as Anthony (5) says:

> There are two main types of ear trauma, one where the symptoms are part of the symptom complex of caisson disease and produced by nitrogen bubbles in the cochlear and vestibular apparatus, the other where they are directly due to the action of the compressed air.

We know that as early as 1900 this distinction was clearly understood for Heller, Mager, and von Schrotter (6) divided their cases of ear trauma in caisson workers into two groups. The first group consisted of cases of temporary deafness and vertigo caused by compression. The second group was composed of the cases which showed "Meniere's syndrome" and in which the aural lesions were thought to be due to nitrogen bubbles.

In 1909 Keays (7) reported on 3,692 cases of compressed-air illness. Of these, vertigo without other symptoms was noted in 113 cases, pains in the ears, hemorrhages from them and temporary deafness in 68 cases, Meniere's symptom-complex in 14 cases and apoplectiform deafness in 2 cases. Two years later Bassoe (8) reported that 87 men of a group of 161 caisson disease cases gave a history of ear affections, 33 complained of dizziness, and rupture of the drum occurred in 2 cases.

Silberstern (9) in 1912 reported on 190 cases of caisson disease including 11 cases of hyperemia of the ear drum, 12 of hemorrhage into the tympanum, 3 cases of myringitis and 1 case of suppurative otitis media. In the same year Hill (10) wrote his book on diving in which he says:

> The cases of ear trouble were of two kinds: 1. Cases of temporary deafness and vertigo, lasting not more than 8 to 14 days, and caused by nonequalization of the pressure on either side of the drum during compression. The tympanic membrane showed signs of congestion, and there appeared in some cases hemorrhages either in its substance or in the middle ear. Bloodstained sputum might be coughed up from the back of the throat, the blood coming from the Eustachian tube. 2. Cases of Menieres Complex, vertigo, vomiting and deafness—symptoms which might persist indefinitely, and were caused by lesions produced by air bubbles either in the central tracts of the cochlear vestibular nerve or in the internal labyrinth of the ear.

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Anthony (5) in his excellent study of 70 cases of compressed air injuries to the ears and accessory sinuses occurring in the Memphis tunnels reports that

> Pain occurred in each of the 70 cases of compressed air injuries that I have seen. Eighteen cases complained of coughing up bloody secretion or of having a bloody discharge from the nose, 19 cases complained of vertigo, 7 cases complained of severe tinnitus, 3 cases showed nystagmus which cleared up within 1 week, and 1 case complained of double vision, but the diplopia lasted only 2 or 3 days. Thirty-four cases complained of marked deafness in one or both ears. Fifty-five of these cases gave a history of having had an upper respiratory infection before entering the tunnel of compressed air, and on examination, I found that at least 95 percent of the cases had evidence of an upper respiratory infection.
>
> Sixty-nine of the seventy compressed air injuries had ear injuries. The injury was bilateral in 31 cases and affected only 1 ear in 38 cases. There were 52 cases of acute congestion of the ear drum, 23 cases of hemorrhage in the drum, 19 cases of perilabyrinthitis, 9 cases of otitis media, purulent acute, in each of which it was necessary to incise the ear drum, and 2 cases of acute mastoiditis.

The question of rupture of the tympanic membrane is one of great interest. All those working with compressed air have seen cases and those reporting in the literature all agree that it does occur. Dewatripont (11) reports that

> Because of too rapid compression and also decompression, 18 have suffered a rupture of both tympanic membrane, 3 of 1; at least the latter said to us that the blood drained from but 1 ear, but it is possible that the drum of the other was ruptured also without external drainage of the blood being produced.

This quotation brings up a most interesting problem, for he evidently is assuming that because there is frank hemorrhage from the external ear there must be a rupture of the tympanic membrane. This is in error, for it frequently occurs that there is a hemorrhage into the tympanic membrane with disection of either the very thin outer epithelial layer or the equally thin inner layer from the middle fibrous layer, and on occasions there is a rupture of either of these thin covering membranes allowing frank hemorrhage without a complete rupture through the entire tympanic membrane. As was noted above, Silberstern (9) reported "12 hemorrhages into the tympanum" but he does not mention a single case of complete rupture of the drum. As noted earlier in this paper, hemorrhagic blebs and air bubbles have often been observed in the drum membrane itself. Blood has been noted coming from the external canal or from a eustachian tube, and, upon examination, no complete perforation of the drum could be demonstrated. This is not to say that perforation cannot occur for it does; but it is simply a warning not to assume a complete perforation because of hemorrhage. Guttich (12), (13), (14) presents animal experimental work and observations on men to prove that in rupture of the ear drum while diving or swimming under water, there

is a flow of water into the middle ear causing such marked dizziness and loss of balance that without outside help the individual would not be able to make his way to the surface and would drown. "That death due to this type of vestibular imbalance is possible in swimmers cannot be doubted." He advises great care in deep diving especially in cold water and the wearing of oiled cotton in the external auditory canals. Van Dishoeck (15) has developed a pneumophone for the measurement of resistance of eustachian tubes in caisson workers.

United States naval records on this condition are incomplete since many never report for treatment, others are treated as ambulatory patients and are not admitted to the sick list even for record, and others are given the disease diagnosis of Otitis Media. The proper diagnosis for these cases is rupture, traumatic, tympanum No. 2548, Speciality letter U, for diving and submarine escape appliance. The Annual Report of the Surgeon General, United States Navy lists no such injuries for 1935, 1936, 1937, and 1938 but does list two cases for 1939. Vail (16) in 1929 quoted from a letter from the Surgeon General of the Navy saying that there were "no admissions to the sick list for damage to the ears that could be considered due to diving activity." He also quotes Lt. Comdr. G. H. Mankin with whom we agree when he says:

> As is well known, the incidence of damage to the ear drums among diving personnel of the Navy is much greater than would appear from a study of the vital statistics published in the Surgeon General's annual report. This state of affairs obtains for one of two reasons: the condition is overshadowed by some other incident of diving more serious in nature or the ear damage is insufficient to warrant placing the diver on the sick list with the sending of the customary notice to the Bureau of Medicine and Surgery.

Vail himself reports two cases of complete rupture of the drum, one in three places with bleeding from the nose and from the affected ear. Proper recording and reporting of this condition is of extreme importance not only because of the danger of immediate complications but also because of the frequently associated diminution of auditory acuity.

As noted in the illustrative case histories; complications range from otitis media to mastoiditis but the most frequent and also the most serious complication of aero-otitis media is the associated loss of auditory acuity. This is completely considered in section B of this paper, but it is important at this time to emphasize that the loss may at times be sufficiently great to be disabling; and that it may take as much as a month to clear in favorable cases and in some cases may never return to normal.

Treatment of a conservative nature has been most effective in our series. In some of the first cases treated an attempt was made

to equalize the air pressure by the use of an eustachian catheter or the Politzer bag but no more relief was obtained than by instillation of warm soothing oil to the ear. Anthony (5) tried inflation of the eustachian tubes in 25 percent of his cases but found no benefit and, in fact, says it is contra-indicated because of the frequently associated inflammation of the eustachian tube. At the present time "auralgan" in the external ears and shrinking of the mucous membrane of the nose by spraying with an ephedrine inhalant is used exclusively in the treatment of these ears with excellent results. Manigan (3) recommends conservative treatment and advises against inflation or myringotomy, even in the presence of a bulging drum membrane. For the restoration of normal hearing, time is the only treatment available, as it is necessary to await the organization and final absorption of the blood and serum in both the drum membrane itself and in the inner ear.

The alleviation of this condition by the inhalation of helium-oxygen mixtures was advocated in 1939 by Lovelace, Mayo, and Boothby (2) because of the increased speed with which it would diffuse through the eustachian tube into the middle ear. Crosson, Jones, and Sayers (17) in the work on the Queens Midtown Tunnel in New York City found that 82 out of 84 locked out because of blocked ears were able to reenter the pressure chamber without difficulty after breathing a helium-oxygen mixture for 3 minutes. Requarth (18) found not only that great immediate relief was obtained by breathing the helium-oxygen mixture but that he had much less "infection and suppuration" in the ears of the helium treated cases.

PREVENTION

Prevention rests largely upon careful physical examination to eliminate men suffering from any acute or chronic upper respiratory infection, common head cold, acute or chronic tonsillitis, pharyngitis, sinusitis, otitis, or marked obstruction of the nasal passages by polyps or deviated nasal septum.

The use of the helium-oxygen mixture during the taking of the pressure was advocated by the authors already quoted and by Hall (19) and has proven to be of undoubted value in assisting the men to take pressure without injury to the tympanic membrane.

Educational measures leading to a complete understanding of the value of swallowing, yawning and the use of the Valsalva inflation of the ear are of distinct value and should never be neglected.

If extensive pressure exposure is anticipated, a preexposure audiometric study should be made both as a safeguard to the workman and to the employer.

SUMMARY

A study of 152 cases of aero-otitis media occurring in men undergoing submarine escape training is presented, with complete illustrative case histories.

The anatomy, physiology, etiology, symptomatology, pathology, treatment and phophylaxis are discussed in some detail.

Special mention is made of the necessity for accurate reporting of these cases because of the complication of diminished auditory acuity.

SECTION B

HEARING LOSS DUE TO EXPOSURE TO INCREASED AIR PRESSURE

A. Acute Loss.—The acute hearing loss as pointed out in section A, is usually part of the picture of aero-otitis media and results from damage to the middle ear occurring when the individual is unable to equalize the air pressure in the middle ear. This is most often caused by temporary or permanent nonpatency of the eustachian tube. In these cases, the hearing usually returns to normal within a few days but may be delayed for months in cases of severe damage and, in some cases, complete return to normal never occurs.

TABLE 1.—*Hearing loss in terms of decibels or sensation units*

Frequency (cycles)	128	256	512	1,024	2,048	4,096	8,192
Aero-Otitis Media	17.3	22.6	21.5	20.0	20.8	35.6	32.3
Our normal—Identical ages	−0.3	4.7	6.7	−0.3	8.1	9.7	8.6
Our normal—Entire group ages 25–34	1.2	4.7	7.1	−0.4	5.6	14.0	16.3

As will be noted by reference to table 1 and as is shown in figure 1, there is an almost uniform loss of 20 decibels for each frequency between the acute aero-otitis media cases and the normal groups. That this 20-decibel loss was of the conduction type of deafness was demonstrated by both audiometric and tuning-fork studies. Tinnitus was present in a number of cases. The degree of damage observed by otoscopic examination was not consistently reflected in the loss of hearing as determined by audiometry. However, it is probable that were it possible to see the midlde or inner ear, damage would be seen to more closely parallel the hearing loss. As pointed out by Requarth (18):

> In cases of more severe otitis the middle ear is filled with serosanguineous fluid, the drum is a dark bluish red and there is a middle-ear type of deafness. The less severe disorders subside in 24 to 48 hours, the drum resumes

[1] Part I. United States Naval Medical Bulletin. 40: 27–42, Jan. 1942; Part II. United States Naval Medical Bulletin. 40: April 1942.

its normal appearance, and the hearing is unimpaired. Aero-otitis media associated with much fluid in the middle ear resolves slowly over a period of several days to several weeks. Hearing returns as the fluid resolves. In a significant number of patients the fluid becomes infected, perforation occurs, and typical suppurative otitis media results.

Hearing loss in a number of cases increased on the second and third days. This may be explained by coagulation of the extravasated blood in the ear drum and/or the middle ear, causing de-

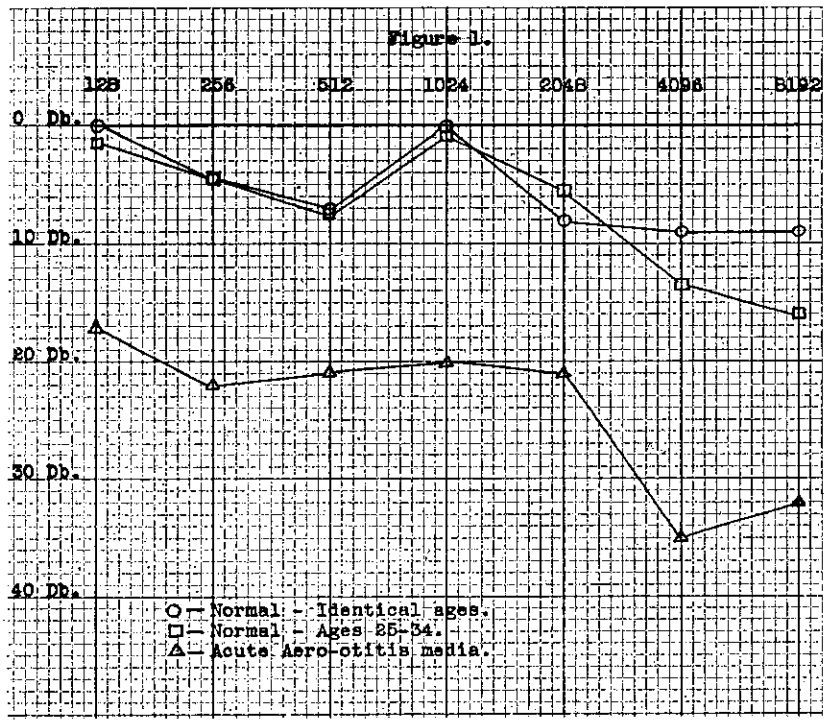

FIGURE 1.—Acute hearing loss associated with acute aero-otitis media as compared with normal groups. The "aero-otitis" curve is the average of 18 recent aero-otitis media cases tested for auditory acuity. The "same age" normal group is the average hearing found in a like number of men of identical ages taken from our general "normal" groups. The other normal group is our entire normal or control group for "ages 25–34."

creased mobility and difficulty of sound transmission. Another consideration is that damage to the drum and middle ear is caused by partial or complete blockage of the eustachian tube and in the attempt to take the pressure there is trauma which causes increased swelling of the mucosa in or around the naso-pharyngeal opening of the eustachian tube tending to produce complete occlusion. With this condition existing there will follow absorption of the oxygen from

the air trapped in the middle ear, and this in turn will cause a cupping effect which will lead to further damage and contraction of the drum causing increased pressure on the ossicles. This may be severe enough to not only cause fixation of the chain but to jam the stapes into the oval window causing damage to the inner ear. The tinnitus, experienced by many, may be caused by this damage or may be an air-pressure phenomenon. This increased loss on the second and third day is well demonstrated in the case of M. L. W. shown in figure 2.

The case of J. D. S., figure 3, clearly demonstrates the fact that loss of auditory acuity is associated with aero-otitis media caused by failure to equalize air pressure, for in this case the right ear was not damaged in the least and suffered no auditory loss, whereas the left ear was damaged on three attempts at taking air pressure and showed marked loss of auditory acuity. Only the left ear is shown in figure 3.

That severe damage to the middle ear and the ear drum leads to marked loss of auditory acuity is shown by the cases of Dewatripont (11).

He reports 18 cases having suffered a rupture of both tympanic membranes and 3 of 1, due to "too rapid compression and also decompression." Of this group, "progressive deafness was started with all of them; 5 have a slight loss of hearing on 1 side and a medium or 5 percent loss on the other; 6 have a bilateral medium loss of 10 percent; 3 in 1 ear a medium loss and in the other a sharp loss, 15 percent; 2 having in 1 ear a sharp hearing loss and in the other a remarkable loss, 20 percent; 1 with marked tinnitus, 25 percent; 1 does not perceive in any manner the whispered voice at more than 10 centimeters and the conversational voice at more than 50 centimeters, therefore, attaining a bilateral deafness quite complete, 30 percent; 1 does not hear the watch nor the whispered voice, nor any tuning fork, nor even the conversational voice near to the ears and must be considered as attaining a complete bilateral deafness, 40 percent; and 1 has on 1 side a sharp hearing loss and on the other complete deafness, 50 percent; and also is subject to intense and frequent vertigo."

It should be noted that the diagnosis of perforation was made in several of these cases from a history of hemorrhage and we know that hemorrhage may occur in acute aero-otitis media without complete rupture of the drum.

Although in the cases presented in this paper the damage has been caused by pressure in excess of one atmosphere, it is equally likely to occur, as pointed out by Armstrong and Heim (1), in aviators upon too rapid return from a rarified atmosphere to atmospheric pressure. It seems certain that loss of auditory acuity must also be associated with damage to the ears under these conditions. In 1935, Armstrong (21) in reporting a free fall in space, reported an apparent diminution of hearing acuity probably due

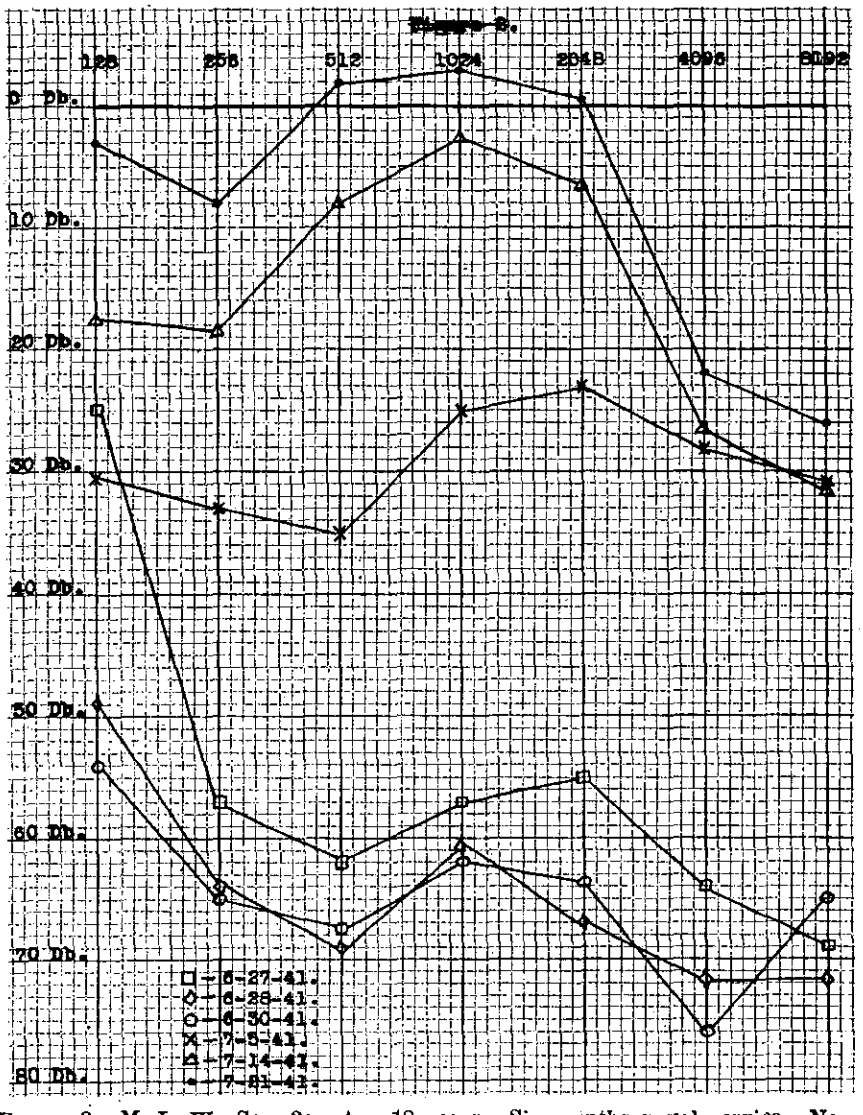

FIGURE 2.—M. L. W., Sea. 2c. Age 18 years. Six months naval service. No submarine duty and no history of previous acoustical trauma or predisposing disease. Failed in an attempt to take pressure on 6-27-41 because of pain in both ears, necessitating locking out at 22 pounds. Both ear drums showed marked congestion with engorgement of blood vessels and marked retraction. The original audiogram done on the same day shows an average loss of 55.6 db for all frequencies which is a remarkable loss but, on the second day (6-8-41), there was an additional loss amounting to an average of 9.1 db making a total average of 64.7 db for all frequencies. As will be noted, there was a substantial gain in auditory acuity during the first week; however, almost a month elapsed before return to normal and even then there was not complete recovery for the frequencies 4096 and 8192.

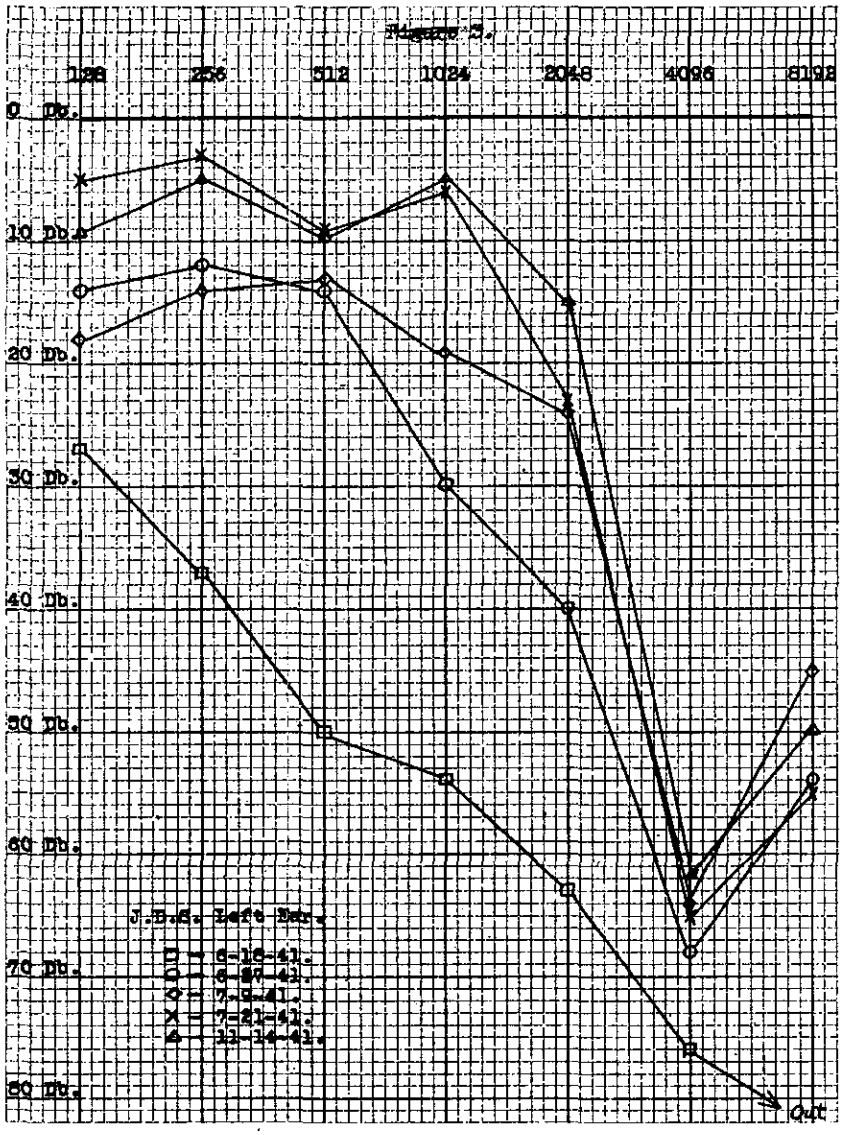

FIGURE 3.—J. D. S., Sea. 2c. Age 17 years. Six months naval service. No history of auditory trauma or predisposing disease. Failed pressure attempt 5–27–41 because of pain left ear. Failed second attempt 6–4–41 again pain left ear. Third attempt 6–17–41 failed as above. Left ear otoscopic examination revealed marked congestion, actual hemorrhage into drum and bubble formation. Tinnitus—frequency 9747 amplitude plus 10 db was an early and distressing symptom. The right ear remained normal at all times both otologically and by audiogram. This figure presents five of many audiograms taken in this case. It will be noted that although the recovery has been marked and is almost complete in the middle and lower frequencies, on the two higher frequencies marked loss still exists after a period of 5 months, and the prognosis is unfavorable for complete recovery.

to "atmospheric conditions." In 16 cases presented by Lovelace, Mayo, and Boothby (2) experiencing difficulty with the ears during rapid descent from a high altitude, subjective deafness was a symptom in 7, 1 complained of tinnitus, and all experienced a feeling of fullness or pain in the ears. This loss of hearing in the aviators becomes of particular significance during flight when voice communication is necessary.

Great care should be exercised in all activities where individuals are exposed to high pressure air in order to preclude this damage. As stated in section A, careful physical examination, particularly of the ear, nose, and throat, and proper instruction in the methods of clearing the ears are of prime importance.

It is fully realized that no fine line of demarcation can be drawn between acute and chronic or permanent loss. Acute damage may result from aero-otitis media and if not severe it may clear quickly and completely. On the other hand, the damage may be sufficiently severe that permanent loss will result. In like manner the damage purported to occur as the result of compressed-air illness is usually reported in the literature to be acute or sudden in its onset, but by most authors is said to be more apt to result in permanent loss of hearing than the damage caused by too rapid compression. For this reason the subject of hearing loss due to compressed-air illness is discussed under the heading of permanent loss.

B. Permanent Loss.—As pointed out above, permanent damage to hearing, particularly in the higher frequencies, may result in any case where damage to the middle ear has been extensive. This is well illustrated by the two cases (figures 2 and 3) presented under acute loss. Boot (22) reports 13 cases of hearing loss in caisson workers and says:

> The most characteristic result of work under compressed air is a loss of the upper tone limit corresponding in type to the loss of hearing due to working in extremely noisy places such as, for instance, in boilermaking shops. It appears to be a slow degeneration that, starting at the upper limit of hearing, gradually extends downwards. The amount of deafness of this type occurring in caisson workers corresponds to some extent to the time the patient has spent working under complessed air.

He does report that some of the men were "blocked" several times, i. e., failure to equalize pressure resulting in aero-otitis media, but still credits routine pressure exposure as the cause of the deafness.

TABLE 2.—*Hearing loss in terms of decibels or sensation units*

Frequency (cycles)	128	256	512	1,024	2,048	4,096	8,192
Divers—"Pure" mean age 30.3 years	2.3	8.0	11.9	4.6	12.0	27.8	24.5
Our normal—Ages 25–34 years	1.2	4.7	7.1	—0.4	5.6	14.0	16.3
Divers—"Misc." mean age 37.3 years	6.0	14.7	17.0	9.2	21.3	46.3	39.3
P. H. normal—Ages 35–44 years	3.8	8.6	8.0	3.0	4.2	26.2	21.7

Were permanent loss of hearing likely to occur from exposure to high-pressure air, *per se*, then deep-sea divers would show marked diminution of auditory acuity, for no group of individuals in the naval service are exposed to high-pressure air more frequently than are deep-sea divers. Yet, in our experience, they do not develop extensive loss of hearing, due undoubtedly to the fact that as a group they encounter little or no difficulty in equalizing air pressure and, therefore, do not develop aero-otitis media and its associated damage to the mechanism of hearing. This is illustrated by table 2

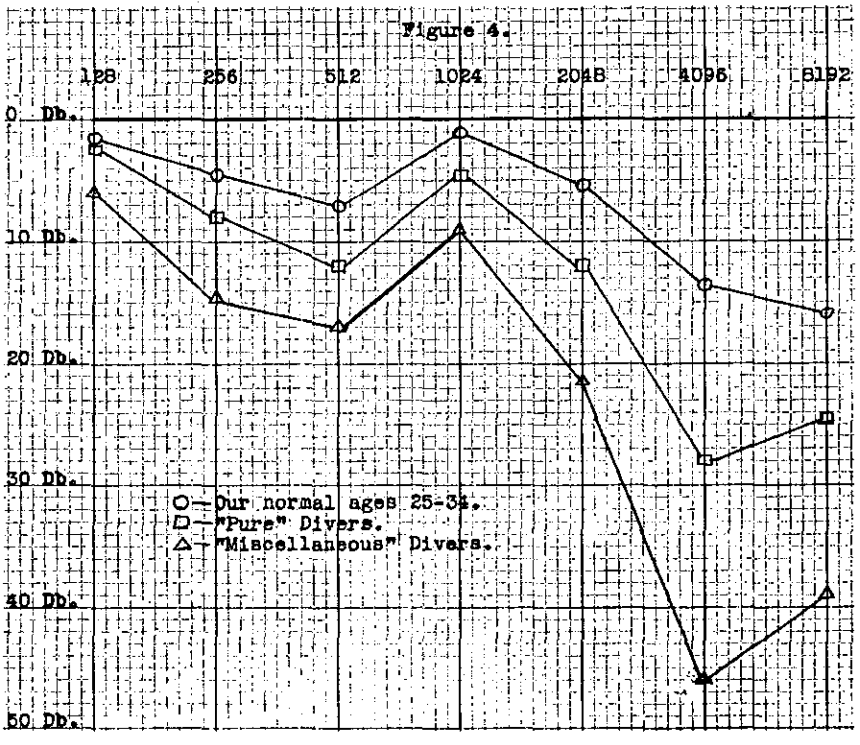

FIGURE 4.

and figure 4 where the loss of auditory acuity to the "pure" divers is very little greater than would be expected for their age alone. Even this slightly increased loss, we believe, is due to certain individuals in the group who have, on occasion, had difficulty in equalizing pressure and show considerable loss which, of course, adversely affects the general average for the divers' group as a whole. The "miscellaneous" group, as would be expected, because of additional trauma, infection, and disease, shows a somewhat greater loss.

The authors have, during the past 12 years, consistently been exposed to high-pressure air up to 10 atmospheres absolute and yet

the average auditory acuity for one of us is 1.0 db above the normal for all frequencies and the other shows only an average loss of 5 db for all frequencies, which is less than would be expected for his age group. Thus, it is again demonstrated that the taking of pressure is, in itself, not the cause of loss of auditory acuity, but that such loss is associated with damage to the middle ear due to inability to equalize air pressure. The author, whose hearing is most acute, has had mild compressed-air illness on three occasions but has never had difficulty in taking air pressure; whereas, the other has, on two occasions, had slight aero-otitis media due to inability to equalize pressure and has never had compressed-air illness.

"Pure" cases showing permanent damage are presented in figures 5

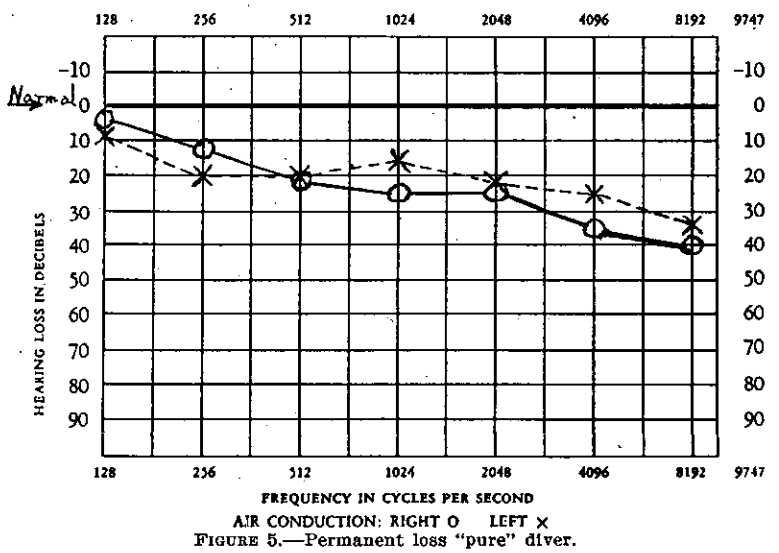

FIGURE 5.—Permanent loss "pure" diver.

A. J. V., T. M. 1c. Age 35 years. Seventeen years naval service. Ninety-six months diving duty. No submarine service. Had mild fungus infection left ear. Had no difficulty taking pressure at any time. Both ear drums dull. Watch tick right 32/40. Examination otherwise negative.

and 6. Neither of these cases shows very marked loss of hearing although by comparison with figure 4, it will be noted that both are below the average hearing loss for the entire group. The two "miscellaneous" cases presented in figures 7 and 8, as would be expected, show more marked loss. One of them, E. A. C., was dropped to a depth of 90 feet without being checked, and he suffered a severe injury to his right ear which undoubtedly caused the permanent loss of hearing in that ear. The other case, J. C. H., was also dropped, causing rupture of his left ear followed by acute otitis media. This is also reflected in extensive loss of hearing in the left ear. Both

of these men must have suffered from acute aero-otitis media as a result of these accidents.

The association of deafness with compressed-air illness has for years been reported in the literature. However, differentiation between the damage caused to the ears by too rapid compression as compared with damage following the development of compressed air illness has not been clearly made. Among the earliest authors to make a clear distinction were Heller, Mager, and von Schrotter (6) who divided their cases of ear trauma in caisson workers into two groups. The first group consisted of cases of temporary deafness and vertigo caused by compression. The second group was com-

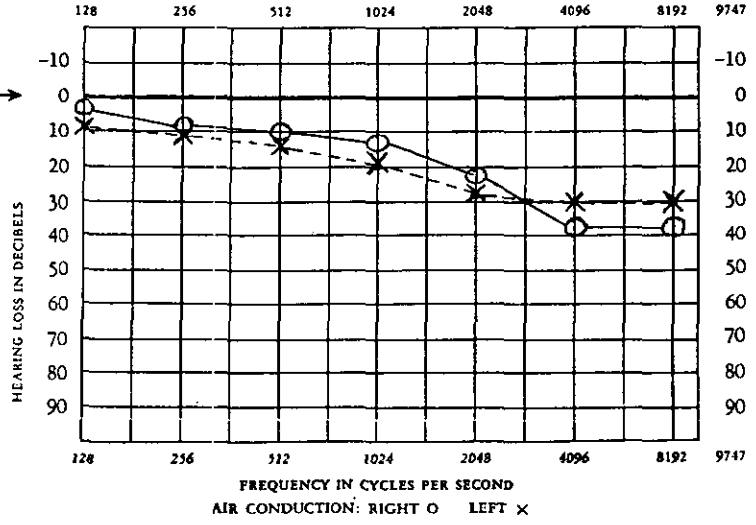

FIGURE 6.—Permanent loss "pure" diver.

C. N., B. M. 1c. Age 29 years. Twelve years' naval service. Sixty-six months' diving duty. No submarine service. *Had no difficulty taking pressure at any time.* "Lung" training twice. Both ear drums dull and retracted. Watch tick right 26/40. Left 28/40. Examination otherwise negative.

posed of the cases which showed "Meniere's syndrome" and in which the aural lesions were thought to be due to nitrogen bubbles.

Lestienne (23) reports a most interesting case which must be considered to be due to bubble formation:

> Worked 7 hrs. in a caisson depth 24 meters . . . decompression lasting 35 *minutes . . . in free air 20 minutes . . .* stricken sharply with intense vertigo . . . vomiting . . . violent tinnitis, especially left ear . . . rapidly progressive and bilateral deafness . . . could not hear yells.

His condition improved somewhat but in left ear 7 months later there was still marked deafness. Although he says that his cases are all due to errors in decompression, he points out that damage

may be caused by injudicious compression but that these accidents are not either as common nor as serious in the production of deafness.

Bunch (24) reports two cases of almost total loss of hearing as caisson deafness but insofar as his report is concerned, neither compressed-air illness nor aero-otitis media were considered as causative factors. Vail (16) reports cases of deafness due to errors in both compression and decompression, and he says that in the first group the hearing loss may be temporary or permanent, whereas in the second group they are usually permanent. Malan (25) studied the acoustic function both before and after compression and reports the damage produced upon the physiological function of the ear.

In figures 9 and 10, we present two cases of men who have had

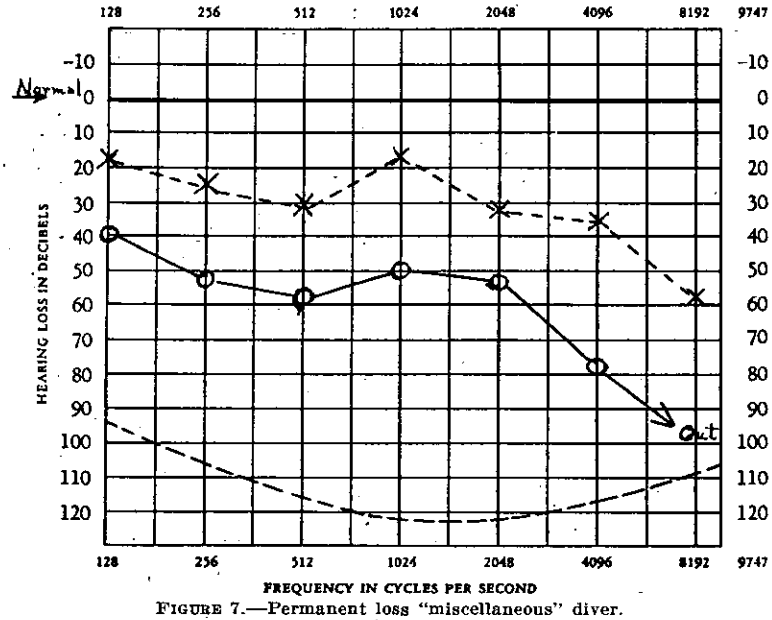

FIGURE 7.—Permanent loss "miscellaneous" diver.

E. A. C., C. T. M. Age 39 years. Seventeen years naval service. Four-inch gun fired over his station caused "ringing" and partial deafness for about 2 hours. Dropped to 90 feet by tenders—right ear bled and sometime later had "boil" in ear canal. Unable to take pressure only once and then quit diving. Right ear drum dull, scarred, retracted and thickened. Left drum dull and thickened. Watch tick right contact only, left 2/40. Whispered voice right 13/15. Otherwise normal.

most severe compressed-air illness several times and who have been exposed to high air pressure for periods of 7½ and 8 years, respectively, and yet show no general loss of auditory acuity, despite numerous complicating conditions reported in their histories. J. M. had serious difficulty in equalizing pressure once and shows a char-

acteristic loss in frequencies 4,096 and 8,192. The two cases here presented still have serviceable hearing far better than most authors lead one to suspect would result from compressed-air illness such as these men have experienced, to say nothing of their long and oft-repeated exposures to compressed air up to and including 10 atmospheres. We also have other audiograms in our series of divers who have had extensive pressure exposure and whose audiograms approximate the normal throughout. These are included in table 2 and figure 4.

The extensive report of Keays (7) substantiates our contention

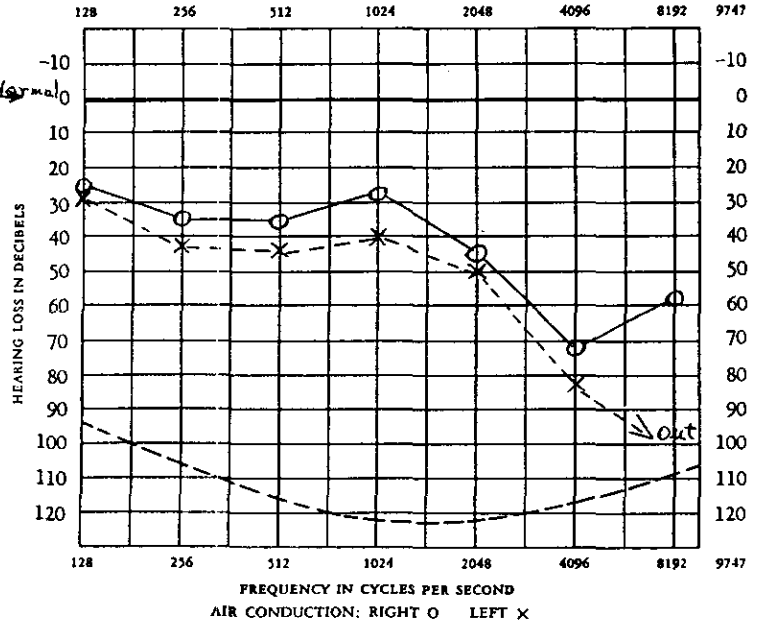

FIGURE 8.—Permanent loss "miscellaneous" diver.

J. G. N., C. T. M. Age 44 years. Twenty-five years naval service. Ten years diving duty. No submarine service. Father partially deaf at age 43. Dropped by tenders to bottom too rapidly causing rupture left ear drum—bled freely and afterward became infected. Some drainage for several years. Noted some deafness for past several years. Both ear drums dull and retracted. Left scarred. Romberg—slight sway. Weber lateralizes to the right. Watch tick right 5/40, left contact only. Whispered voice right 7/15, left 1/15. Spoken voice right 10/15, left 5/15. Coin click right 20/20, left 2/20. Physical examination otherwise negative.

that compressed-air illness rarely is responsible for deafness for in 3,692 cases of "caisson illness" vertigo without other symptoms was noted in 113, pain in the ears, hemorrhages from them and temporary deafness in 68 (*aero-otitis media*), Meniere's syndrome symptom-

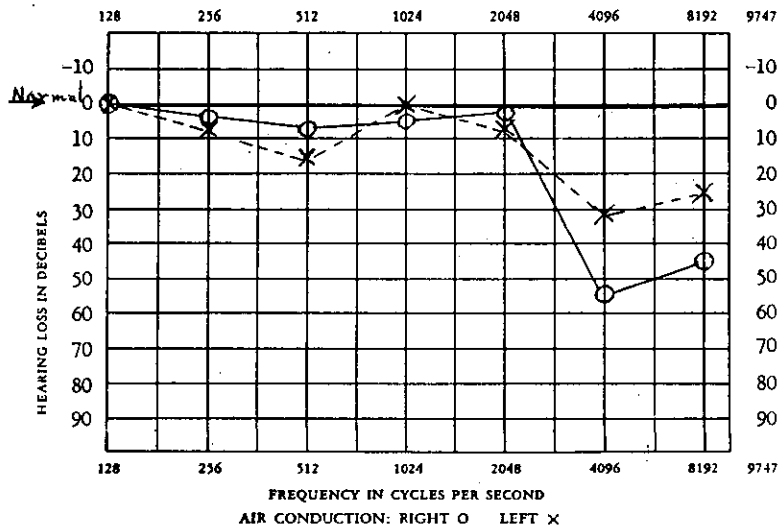

FIGURE 9.—Permanent loss (compressed-air illness) diver.

J. M., C. T. M. Age 29 years. Twelve years naval service. Ninety months diving duty. No submarine service. (Twenty-four months instructor in "Lung" training included in diving duty.) Deafened for a few minutes several times from gunfire. Difficulty in taking pressure only once. Abscess—left ear, ruptured spontaneously, no treatment. Compressed-air illness of a severe nature several times. Left ear dull and slightly retracted. Watch tick right 12/40, left 16/40. Examination otherwise negative.

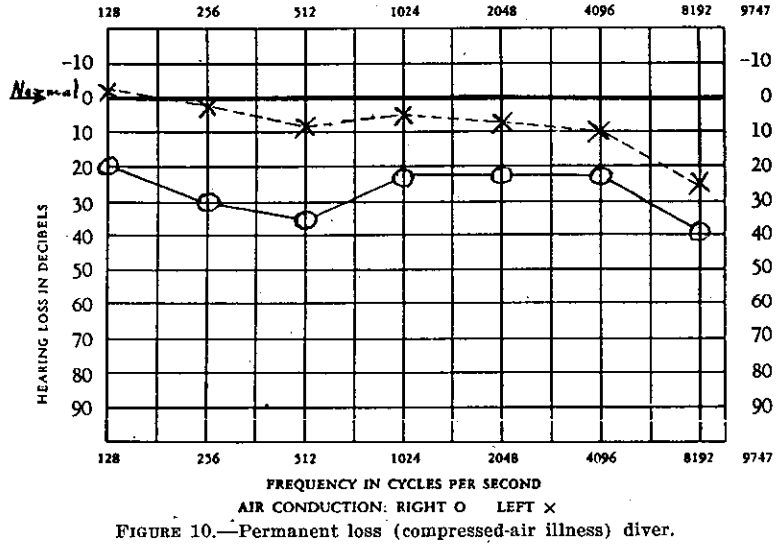

FIGURE 10.—Permanent loss (compressed-air illness) diver.

O. L. C., C. B. M. Age 37 years. Seventeen years naval service. Ninety-six months diving duty. No submarine service. (Twenty-four months "Lung" training instructor included in diving duty.) Deafened for 20–30 minutes several times from gunfire. Grandmother deaf in old age. Had compressed-air illness of a severe nature several times. Both ear drums normal. Watch tick right 20/40, left 20/40. Examination otherwise negative.

complex in 14 and apoplectiform deafness in but 2 cases. Thus at the most but 16 cases out of 3,692 can be counted as having suffered loss of hearing due to compressed-air illness.

A report from the United States Navy experimental diving unit, (26) presented 46 cases of experimentally produced compressed-air illness in which every factor was completely studied and controlled. In this group there were no 2 cases alike and yet not 1 single case complained of or developed any loss of auditory acuity. This is not a large series but if deafness were such a common complication at least 1 case would be expected to occur.

The conclusion is inevitable that whereas deafness may result from compressed-air illness it is an extremely rare occurrence. It is also certain that exposure to compressed air in itself does not adversely affect the hearing. In other words most of the deafness found to be associated with work under compressed air is due to damage to the ears because of failure to properly equalize air pressure in the middle ear—aero-otitis media.

SUMMARY

Data have been presented showing acute loss of auditory acuity associated with aero-otitis media.

Exposure to air pressure, in itself, was shown to have little, if any, effect in producing loss of auditory acuity.

Compressed-air illness was shown to be a rare cause of loss of auditory acuity.

The positive relationship between loss of auditory acuity due to damage to the ears of divers during exposure to high pressure air and the same type of damage to aviators during too rapid return to atmospheric pressure from a rarified atmosphere was suggested.

The importance of great care in the physical examination and of proper instruction of the men prior to the "taking of pressure" was stressed.

Further studies concerning naval hazards to hearing are in progress and will be presented as the work is completed.

To be continued

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TRAUMATIC CONDITIONS OF THE EAR IN WORKERS IN AN ATMOSPHERE OF COMPRESSED AIR*

HARRIS H. VAIL, M.D.
CINCINNATI

For ninety years, the condition known as caisson sickness or disease has been studied by many observers. In 1912, Hill [1] published the historic, physiologic, experimental and pathologic facts about caisson sickness.

In 1896, Alt [2] reported three severe cases of apoplectiform labyrinthitis in caisson workers. A workman, an hour after being subjected to a pressure of 2.2 atmospheres for more than two hours, experienced a sudden onset of severe pain in the ears, vertigo and absolute deafness. Another workman, within a few minutes after leaving the air lock, experienced the sudden onset of severe pains in the chest, serious collapse and total deafness. A third workman had cyanosis, dyspnea, deafness and marked vertigo.

In all of Alt's cases, the Weber test was referred to the ear less affected. The return of hearing was slight, and the tympanic membranes were not ruptured. However, he quoted a case reported by Moos, in which a caisson worker suddenly became deafened, with traumatic rupture of both tympanic membranes and bilateral hemorrhagic labyrinthitis.

In 1900, Heller, Mager and von Schrötter [3] divided their cases of ear trauma in caisson workers into two groups. The first group consisted of the cases of temporary deafness and vertigo caused by compression. The second group was composed of the cases which showed "Ménière's syndrome," and in which the aural lesions were thought to be due to nitrogen bubbles.

In 1909, Keays [4] reported 3,692 cases of caisson illness. Of these, vertigo without other symptoms was noted in 113, pains in the ears,

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* Read at the Sixty-Second Annual Meeting of the American Otological Society, Atlantic City, N. J., May 22-24, 1929.

* From the Laboratory of Experimental Surgery, Medical College, University of Cincinnati.

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3. Heller, Mager and von Schrötter, quoted by Hill (footnote 1).

4. Keays, F. L., quoted by Hill (footnote 1).

hemorrhages from them and temporary deafness in 68, Ménière's symptom-complex in 14 and apoplectiform deafness in 2 cases.

In 1913, Boot reported the case of a caisson worker who experienced vertigo and bilateral deafness one week after quitting work.

Boot reported another case in which bleeding from the nose and the left ear took place shortly after the worker emerged from the caisson. Later, vertigo and tinnitus appeared in the left ear.

In 1926, Damant[6] reported 30 moderately severe cases of caisson illness in 5,000 dives, but he did not mention any cases of deafness or ruptured ear drum membranes.

From the Bureau of Medicine and Surgery of the U. S. Navy I obtained a valuable contribution to the subject. In an answer to my inquiry, Capt. E. J. Grow, Medical Director, U. S. Navy, wrote me in 1929 as follows:

> A search of the records of the Bureau of Medicine and Surgery from 1924, to the present time fails to disclose a single admission to the sick list for damage to ears that could be considered due to diving activity.
>
> This, of course, cannot be construed to mean that there have not been instances of such injury. Rather, it would appear that such disability has been too trivial to warrant admission to the sick list, or else such injury was a complication of a more serious condition and therefore did not become a matter of record, except as a notation in the health record.
>
> In the case of an underwater fall, the tympanic membrane may be suddenly ruptured but the attendant "squeeze," which the diver experiences, is the serious condition for which the diver is admitted and returns made to the Bureau.
>
> It is singular that the records for 1924 and since show no admissions for ruptured tympanic membrane in the case of divers who have made descents and have been unable to equalize the pressure on the membrane. It is believed that the attendant pain, which is severe in character, is a safeguard in this condition as it gives ample warning.
>
> A study of the auditory acuity and its decline among divers would be significant if it appeared that this decline was more rapid and more notable than the average in a similar age group not engaged in diving.

The well known subjective sensations in the ears which workers in an atmosphere of compressed air experience have been described by many observers.

In 1898, Lester and Gomez,[7] while in a caisson, found that bone conduction was affected to a greater degree than air conduction, and that the hearing power for air and bone conduction was reduced directly in proportion to the air pressure in the caisson.

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They were of the opinion that a pressure of 0.5 atmosphere was sufficient to cause retraction of the membrana tympani, and 2 atmospheres caused congestion of the malleolar plexus and in some cases caused displacement of the ossicular chain, with resulting tinnitus. As the pressure increased in the air lock, they experienced a slight feeling of fulness in both ears, which was relieved at first by keeping the mouth open. With a further increase of the pressure it seemed as if their ear drum membranes would rupture, and they noticed a high pitched tinnitus but no vertigo. All these symptoms disappeared when they entered the caisson. It was then that the peculiar pitch and intensity of their voices, autophony and difficulty in speaking and the impossibility of whistling were noticed.

Capt. E. J. Grow, M.C., U. S. Navy, Acting Chief of the Bureau of Medicine and Surgery, furnished me with a report from Lieut. Commander G. H. Mankin, M. C., U. S. Navy, to Capt. J. M. Brister, M. C., U. S. Navy, that I have quoted in full.

As is well known, the incidence of damage to the ear drums among the diving personnel of the Navy is much greater than would appear from a study of the vital statistics published in the Surgeon General's annual report. This state of affairs obtains for one of two reasons: the condition is overshadowed by some other incident of diving more serious in nature, or, the ear damage is insufficient to warrant placing the diver on the sick list with the sending of the customary notice to the Bureau of Medicine and Surgery.

Fortunately or otherwise, I am able to cite an incident from recent personal experience. On March 22, 1929, while engaged in submarine escape tests with the "lung" in the 60 ft. mine tank at the Navy Yard, Washington, D. C., it was necessary for Lieutenant Momsen and myself to descend to the bottom of the tank in a diving bell preparatory to escaping to the surface, using the "lung." The diving bell supplied with compressed air was lowered by an electric winch at the surface. By a life line from the bell to the surface we were able to give signals and control the speed with which we were lowered. At about 20 ft. from the surface I began to have slight pain in my right ear. I had had a rather severe head cold for several days but had been able to continue the tests by having a preliminary intranasal treatment designed to shrink the congested mucous membrane, and with this precaution I had had no difficulty in clearing my ears until this particular day. I presume there had been too long a delay between the treatment and the dive. We continued the descent very slowly but by no method could I get air through the eustachian tubes and the pain in both ears became progressively annoying. By signal we asked to have the bell hoisted a few feet. This relieved the pain. On lowering away again the pain reappeared and increased until we reached the 40 ft. level. From 40 ft. on down there was no pain or discomfort, even though the descent was rather rapid. The escape from the diving bell to the surface was made in the routine manner and without discomfort.

After getting out of the water a quantity of bright red blood was blown from the nose. Aside from lowered auditory acuity and the sensation of "talking in a barrel," there was nothing of note in connection with the ears.

I had a somewhat similar experience during the salvage of the U. S. S. S-4 off Provincetown, Mass., in the winter of 1927 when I had to accompany a diver with compressed air illness into the recompression chamber of the U. S. S. Falcon. My left ear did not clear as we increased the pressure in the chamber. I had a

moderate amount of pain, but of course had to continue on account of the condition of our patient. There was subsequent nasal hemorrhage. I thought very little of the incident, and, as I had no one with me at the time who could examine my ear, I never knew what actually occurred.

In the present case I had the ear, nose and throat specialist look at my ears at the time of my next regular appointment for nasal treatment. Much to my surprise, he found both drums ruptured in Shrapnell's membrane and an old scar in the left drum, presumably following the incident on the U. S. S. Falcon. I think one gains from the literature the impression that the pain accompanying the rupture of an ear drum is very severe. From my experience in the two incidents mentioned, I would question this view because at no time was the pain more than quite annoying. It is quite possible that the same lesion produced suddenly would be extremely painful.

Both of my ear drums have healed (one month from the time of their rupture) and there is apparently no diminution in the auditory acuity.

Similar subjective sensations have been described by the divers, Eadie[8] and Ellsburg.[9]

REPORT OF TWO CASES OF TRAUMATIC RUPTURE OF THE TYMPANIC MEMBRANE

Dr. Glenn Adams of Cincinnati referred to me these two cases of traumatic rupture of the tympanic membrane.

CASE 1.—A young colored man, when he left the caisson where he had been working under a pressure of 27 pounds (12.2 Kg.), noticed severe headache, a feeling of fulness and deafness in both ears and bleeding from the nose and the right ear. The following day he was recompressed without relief from these symptoms. The next four days he felt dizzy and experienced severe pains in both ears and the back of the neck. His deafness was unimproved.

When I first saw him a week had elapsed since the accident. He gave a history of having been subject to many attacks of nasal coryza, but he had never noticed any deafness.

The right tympanic membrane showed three distinct recent perforations: a large one directly posterior to the umbo, a smaller one anterior and the third one posterior to the malleus at the level of the umbo. The tympanic membrane was much retracted, with considerable foreshortening of the short process. Anterior to the latter, there was a light reflex. Along the handle of the malleus there was injection, and many fine blood vessels could be seen running down the posterior fold. Shrapnell's membrane was retracted and somewhat congested. There was no drainage of blood or serum from the middle ear. The left tympanic membrane showed no perforations. It did show, however, many blood vessels running down from the anterior and posterior folds and Shrapnell's region, with some congestion of the latter.

The right ear could not hear a whisper, but heard ordinary conversation up to a distance of 2 feet (60.9 cm.). The lower limit was 64 double vibrations and the upper limit was 3.4 with the Galton whistle (normal 0.8). The left ear heard a whisper up to a distance of 2 feet and conversation up to a distance of 14 feet

8. Eadie, Thomas: I Like Diving, Saturday Evening Post, 1928, vol. 201, no. 18.

9. Ellsburg, Edward: On the Bottom, Saturday Evening Post, 1928, vol. 201, nos. 19-22.

(426.7 cm.). The lower limit was 32 double vibrations and the upper limit was 1. The Weber test was referred to the left ear. There was an average loss of hearing in the right ear of 47 per cent and one of 35 per cent in the left ear when tested by the Western Electric 2-A audiometer. The curves of hearing showed a marked depression in 4,096 and 8,192 vibrations.

Nasal examination showed a moderate deviation of the nasal septum with polypoid degeneration of both middle turbinals.

On politzeration, both eustachian tubes were open. For the next two days there was no change in the condition of the patient. A gentle massage of the right tympanic membrane with the Siegel otoscope seemed to improve his hearing slightly, so that he heard a whisper up to a distance of 2 inches (5 cm.) and conversation up to 7 feet (213.4 cm.)

Two days later he was again seen, and at this time the perforations of the membrana tympani were found to be healed. The usual cold caloric test with water at 68 F., with the head 30 degrees forward, produced in the right ear a rotary nystagmus to the left after ninety seconds of irrigation; when the head was put back, the nystagmus became horizontal.

Two weeks after the accident, the right ear heard a whisper 1 foot (30.5 cm.) away and ordinary conversation 12 feet (365.8 cm.) away. The left ear heard

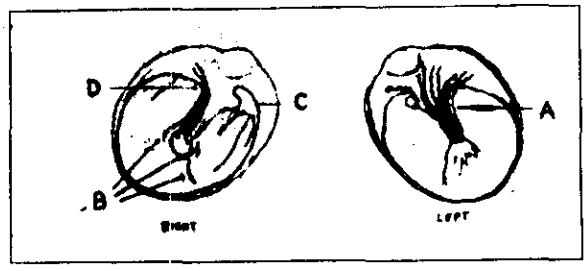

Fig. 1 (case 1).—Diagrammatic sketch of the tympanic membranes. The three perforations of the right tympanic membrane are indicated (*B*) as well as the extent of injection of both membranes (*A*). *C* indicates light reflex.

a whisper at a distance of 14 feet. The hyperemic reaction in the tympanic membrane had disappeared. The man still felt a little dizzy and noticed pain and tinnitus in both ears.

One month afterward, he was able to hear a whisper 3 feet (91.4 cm.) away and conversation at 14 feet. After six weeks, he heard a whisper at 5 feet (152.4 cm.) and the 32 double vibration fork, and by two and one half months the right ear heard a whisper at 6 feet (182.9 cm.) and conversation at 14 feet. The Weber test was referred to the left ear.

CASE 2.—A young man was working in the same caisson under 30 pounds (13.6 Kg.) of pressure. While in the caisson he noticed a buzzing noise in the ears and dizziness, but was able to work for his two hour shift. During the afternoon shift he felt dizzy and sick, and both ears felt stopped up. One hour after leaving the caisson, he noticed some bleeding from the right ear, with severe headache and deafness in that ear. By nightfall the headache had become very severe. I saw him the following day, and in the right tympanic membrane were two perforations with fresh blood draining through them. The largest perforation, which was rather ragged, was situated below the umbo. The other perforation was in the posterior superior quadrant just below the posterior fold.

Shrapnell's membrane was markedly retracted and congested. The tympanic membrane was retracted and was bluish. Dried blood clots could be seen in the external auditory canal. The left tympanic membrane was intact, markedly retracted, and many blood vessels could be seen running from the posterior fold downward along the handles of the malleus.

Comment.—Both ears heard a whisper 14 feet away. The lower limit in the right ear was 48 double vibrations, and in the left 32 double vibrations. The Weber

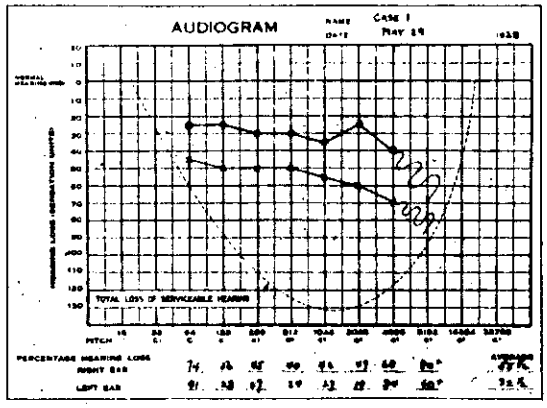

Fig. 2 (case 1).—Audiogram one week after the accident.

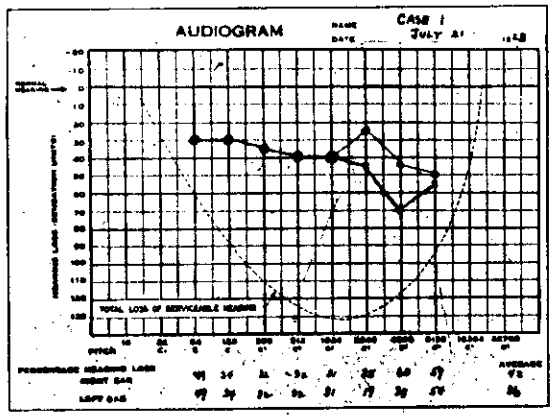

Fig. 3 (case 1).—Audiogram two months after the accident.

test was not referred. The audiometer showed a loss of hearing in the right ear of 18 per cent and one of 10 per cent in the left ear. Most of the loss of hearing was in the lower range.

The second patient was not affected as severely as the first, yet the tympanic membranes in both ears were much alike. The first man had vertigo and marked deafness of the so-called internal ear type, while the second showed no serious disturbances.

COMMENT

The ear may be affected in two ways by the direct action of compressed air. 1. There may be a more or less mild form of trauma when

the damage is confined to the middle ear. 2. There may be trauma when, besides damage to the middle ear, injury is done to the internal ear.

Alexander [10] thought that the inner ear symptoms appearing in caisson workers were caused by hyperemia and small hemorrhages in the internal ear, and that the symptoms might appear acutely after the injury or could at times have a chronic progressive course.

Boot was of the opinion that tubal tympanic catarrh caused exaggerated symptoms in those working in an atmosphere of compressed air; that when the patient showed symptoms referable only to the vestibular apparatus, recovery was complete, and that the most characteristic result when the ears were injured was a loss of a considerable portion of the upper range of hearing with marked lessening of bone conduction. In some cases the organ of Corti seemed to have been suddenly destroyed.

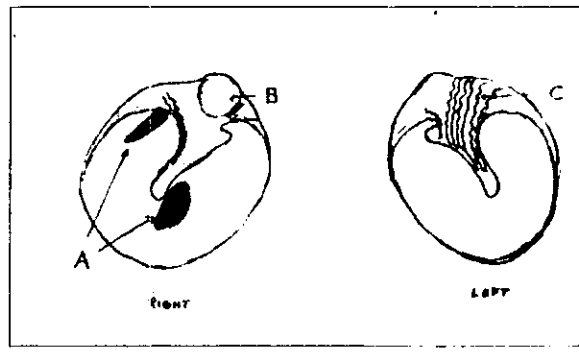

Fig. 4 (case 2).—A sketch of the tympanic membranes, which shows the location and extent of the perforations (bleeding) of the right tympanic membrane (*A*) and the marked vascular injection in both drum membranes (*C*). *B* indicates marked retraction.

Furthermore, Boot believed that the vestibular portion of the labyrinth was more resistant than the cochlear portion.

Bert [11] expressed the opinion that all accidents from the most trivial to those which caused sudden death in caisson workers, were the consequences of the disengaging of bubbles of nitrogen from the blood and tissues when compression has lasted a sufficient time.

Though this is true of caisson disease, it is not the entire cause when the ear is concerned. There are two main types of ear trauma: one in which the symptoms are a part of the symptom-complex of caisson disease and produced by nitrogen bubbles in the cochlear and vestibular

10. Alexander, G.: Die nichteitrigen Erkankungen des inneren Ohres, in Denker and Kahler: Handbuch der Hals-, Nasen- u. Ohrenheilkunde, Berlin, Springer & Bergmann, 1926, vol. 7, p. 553.

11. Bert, P., quoted by Hill (footnote 1).

apparatus, and the other in which they are due directly to the action of the compressed air.

Many authors have felt that the aural trauma during compression was due to the nonequalization of pressure on the two sides of the tympanic membrane. All observers have stated that it was necessary for the caisson workers or divers to swallow or to perform the Valsalva test in order to relieve the painful subjective symptoms experienced in the ears.

Hill believed that the hemorrhages so frequently noted in naked divers were due to a cupping effect in the nasal and ear cavities. If the eustachian tube was open, the pressure would be equalized and no cupping effect could take place in the middle ear. He stated that the diminution of volume of the air in the nasal and aural cavities was

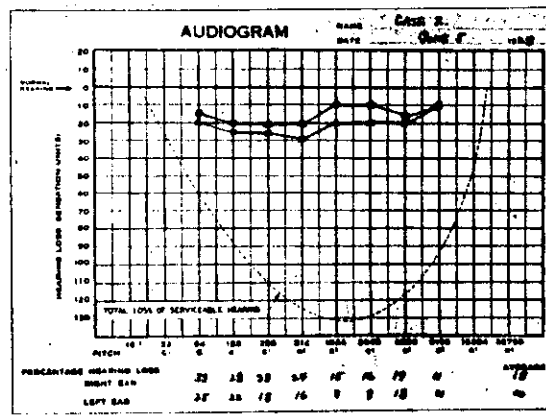

Fig. 5 (case 2).—Audiogram the day following the accident.

greatest in the change from 1 to 2 atmospheres, and that this was the point of greatest danger to the ears. Afterward, at higher pressures, there was little trouble, as the volume of the air in the nasal and aural cavities diminished with proportionate slowness, and enough air passed through the eustachian tube when it had once been well opened.

Von Schrötter stated that on decompression of caisson workers, crackling noises due to the escape of air through the moist eustachian tubes could be heard.

Alt believed that if the eustachian tube was closed there was a negative pressure in the middle ear cavity with a forcing in of the tympanic membrane. The blood vessels enlarged, and a condition resulted that he called "Stauungshyperaemia" of the middle ear and the labyrinth, which could persist beyond the actual time of exposure to the compressed air. He quoted the manometric studies of Politzer and Bezold, who

showed that an increase in the pressure of the middle ear caused an increase in the labyrinthine pressure, while a decrease of the amount of air in the middle ear, caused a fall in the labyrinthine pressure.

EXPERIMENTAL DATA

Hill reported his experiments and those of Lord Haldane, Boycott, Damant and von Schrötter, to prove that not only were the symptoms of caisson illness due to the formation and circulation of nitrogen gas

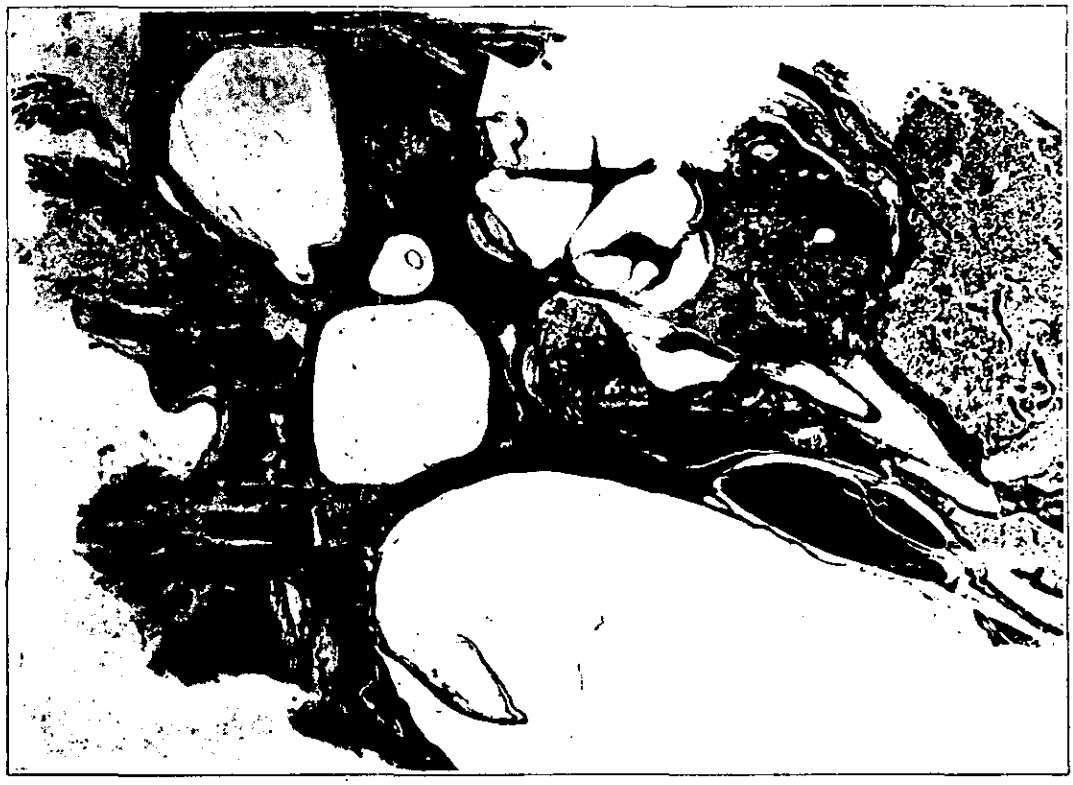

Fig. 6.—Section showing the middle and internal ear of a control rabbit.

bubbles in the tissues of the body, but that the bubbles occurred most frequently in those parts of the body in which the circulation of the blood was the poorest.

Von Schrötter was able experimentally to produce bubbles of nitrogen in the semicircular canals of animals.

Alt observed ecchymosis of both tympanic membranes and two typical cases of bleeding in the middle ears of dogs subjected to a pressure of 5 atmospheres. Examination of the specimens by Professor Gruber showed the mucosa of the tympanic membranes to be intensely

congested with many dilated blood vessels, with similar changes in the middle ear and, in addition, serosanguineous extravasation in the latter.

Microscopic study of the sections of the ears of rabbits subjected to a pressure of 2.5 atmospheres for twenty minutes with rapid decompression and death after four days showed slight engorgement of the blood vessels and perivascular extravasations. The nerve fibers were unchanged.

My experiments were done to simulate actual working conditions as nearly as possible. The animals were subjected to a rapid rise of

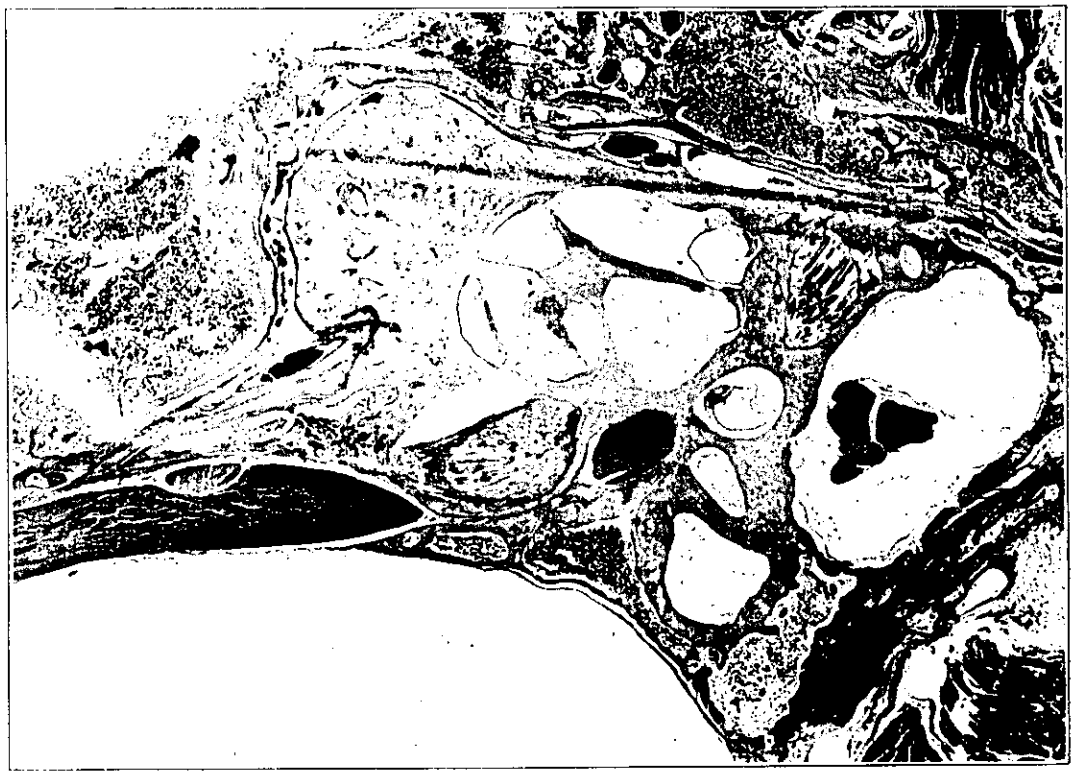

Fig. 7.—Section of the temporal bone of the rabbit in experiment 1. Note the hemorrhage and dilated blood vessel along the malleus and incus. The internal ear showed no hemorrhage.

pressure followed in a few minutes by a gradual reduction of pressure by stages, in order to obtain, if possible, the results of the direct action of the increasing air pressure on the ears. Furthermore, one eustachian tube of each dog was obstructed by a piece of bougie. With the dog under ether anesthesia, the soft palate near its attachment to the hard palate was incised for about 1½ inches (3.77 cm.), and after the edges were retracted to expose the nasopharyngeal orifice of the eustachian

tubes, with a curved hemostat, a quarter inch (0.63 cm.) piece of hard rubber or whalebone bougie was inserted and buried out of sight.

EXPERIMENT 1.—A young white rabbit, weighing 450 Gm., was placed in a compression tank, and by one-half minute a pressure of 70 pounds (31.8 Kg.) was obtained which was continued for one minute. Three minutes later the pressure was reduced to 30 pounds, one and one-half minutes later to 10 pounds (4.5 Kg.) and in another minute and a half to zero. An hour later, the temporal bones were removed and fixed.

At the same time a control rabbit of the same weight and age was killed and its temporal bones fixed.

Fig. 8.—Section of the middle ear of dog 1, showing the site of the bougie in *the eustachian tube as well as the hemorrhage occurring in the middle ear.*

EXPERIMENT 2.—Two young white rabbits, weighing about 450 Gm., were used. Modeling wax was tightly pressed into one external canal of each rabbit, and these rabbits placed in a compression tank. By one minute a pressure of 75 pounds (34 Kg.) was obtained; this was continued for one minute, and then reduced to 40 pounds (18.1 Kg.), in twenty-five seconds. The pressure of 40 pounds was maintained for two minutes, and all the remaining compressed air escaped in forty seconds more. In one rabbit, gross examination of the ears after decalcification showed no macroscopic blood in the middle ears, and in the other rabbit it showed where the wax had been placed, an extravasation of blood into the middle ear cavity but without rupture of the drum membrane.

EXPERIMENT 3.—The right eustachian tube of a dog was obstructed by a piece of bougie, and the dog placed in the tank. The pressure was raised to 75 pounds in one minute, kept there for another minute and then reduced to 40 pounds in twenty-five seconds. It was held at 40 pounds for two minutes, then reduced to 15 pounds (6.8 Kg.) in twenty seconds and held there for two more minutes, and in forty seconds the air was all out. Gross examination after decalcification showed a rupture of the right tympanic membrane and hemorrhages filling both middle ears and mastoid cells.

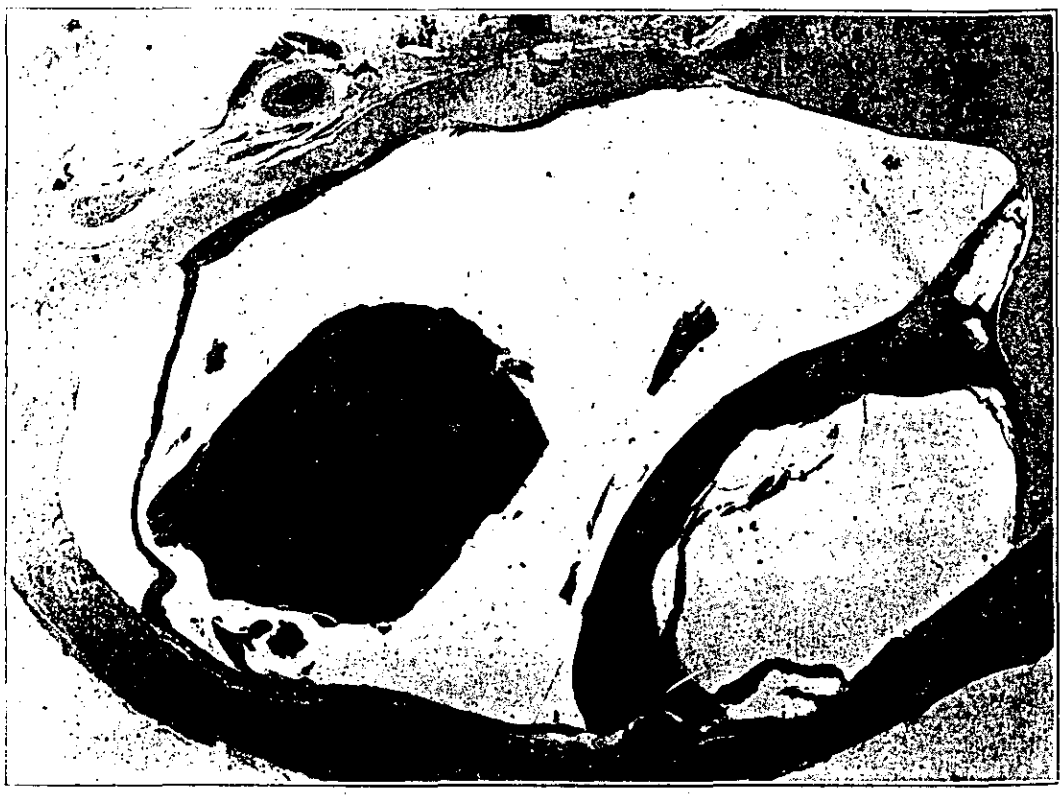

Fig. 9.—Section of the middle ear of dog 2, showing the extent of hemorrhage and the lifting up of the mucous membrane of the middle ear cavity by a hemorrhage.

EXPERIMENT 4.—A one-half inch (1.27 cm.) piece of a flexible bougie was inserted into the left eustachian tube of a dog. Thirteen days later the animal was placed in a compression tank, and the pressure raised to 80 pounds (36.3 Kg.) in one and one-half minutes. This pressure was maintained for one and one-half minutes, reduced to 40 pounds in three minutes and to 12 pounds in one and one-fourth minutes, and all the air was out in another one-half minute. One hour later the dog was killed by ether. Otoscopic examination showed no perforations of the tympanic membranes. Both drum membranes were retracted; the left showed considerable injection along the malleus.

EXPERIMENT 5.—A dog that had had the bougie inserted in the right eustachian tube thirteen days previously was placed in the compression tank, and in one minute and fifteen seconds the pressure was raised to 80 pounds and maintained at that level for one-half minute. It was then reduced to 40 pounds in forty seconds, held there for two minutes and then reduced to 20 pounds in ten seconds. Otoscopic examination showed both drum membranes quite bluish and retracted, without gross perforations.

Fig. 10.—A higher magnification of the section shown in figure 9, showing the mechanism of the elevation of the middle ear mucosa by the submucosal bleeding.

REPORT OF THE MICROSCOPIC STUDY OF THE SPECIMENS BY DR. N. C. FOOT

In every case the lesion was essentially the same, so that the three specimens may be considered together. The constant lesion was a copious hemorrhage into the cavity of the middle ear, apparently originating in small vessels in the submucosa. That this was so was indicated by the fact that the mucosa was lifted off its bony bed and carried well into the center of the cavity, coming to lie on a copious blood clot which was evident, even on gross examination, in every ear examined in this series. In one instance, it was found that this hemorrhage penetrated into the vestibule of the ear, where it filled the cavity almost entirely.

In another section the tip of the bougie introduced through the eustachian canal was seen in situ and the canal is shown in longitudinal section. There was scarcely any difference between sections from the ears that were plugged with eustachian bougies and those not thus occluded; in each instance there had been copious bleeding into the cavity of the middle ear and that of its vestibule.

It may be noted that the structures of the internal ear, the mastoid cells and the bone-marrow of the temporal bone were little altered from their normal appearance; if there were lesions of these anatomic units, they were not evident.

The tympanic membrane was not necessarily ruptured in the dogs. One dog had a marginal perforation on the side where the eustachian tube had been closed.

SUMMARY

Trauma can be inflicted on the middle and internal ears in workers in an atmosphere of compressed air, not only during compression, but also during or after decompression. In the first group the symptoms may be temporary or permanent. In the second group they are usually permanent. Though the cochlear and vestibular portion of the internal ear are both affected, the case reports would seem to show that the cochlear portion of the labyrinth is slower to recover than the vestibular portion.

In the first group, the aural trauma is caused by nonequalization of pressure within and without the middle ear and transmitted to the internal ear with resulting stasis and hemorrhages.

In the second group, the aural lesions are due to bubbles of nitrogen forming emboli or areas of necrosis in the internal ear.

CONCLUSIONS

1. The two cases reported and some experimental observations by the author conform with the clinical observations hitherto recorded concerning aural trauma in workers under compressed air, and suggest the advisability of a careful examination of the nasal sinuses as well as of the ears in the workers.

2. Workers who have suffered traumatic rupture of the tympanic membranes should undergo recompression only in the event that symptoms of caisson illness appear. It would seem advisable that an otologist should be in attendance in such cases.

3. A wide and careful survey must be made to decide whether the percentage of deafness is uniformly high in persons working under compressed air.

I am greatly indebted to Dr. N. C. Foot, professor of pathology at the College of Medicine, University of Cincinnati, for the preparation and study of the microscopic sections, to Dr. W. D. Andrus and Dr. J. L. Donnelly of the Laboratory of Experimental Surgery, Cincinnati General Hospital, for their advice and cooperation and to Mr. James J. Taylor of the Stacey Brothers Gas Construction Company of Elmwood, Cincinnati, through whose assistance the compression experiments were made possible.

OXYGEN TOXICITY

Articles selected by James M. Clark, M.D.
Institute for Environmental Medicine
University of Pennsylvania Medical Center
Philadelphia, Pennsylvania

14

OXYGEN TOXICITY

J. M. CLARK

Any collection of seminal documents in the field of oxygen toxicity would be incomplete at the outset if it did not include the work of Paul Bert (1878; translated 1943). His fundamental studies were comprehensive and his interpretations showed remarkable insight for the time in which he lived. A few years later, J. Lorraine Smith (1899) published the first detailed description of pulmonary manifestations of oxygen poisoning.

In a comprehensive review published in 1945, Bean (1945) summarized essentially all of the previous work in the field as well as the initial studies of his own productive career, spanning the next few decades. Working independently at about the same time, Dickens (1946) and Stadie, Riggs, and Haugaard (1944) published detailed accounts directing attention to the multiple biochemical manifestations of oxygen poisoning.

Behnke et al. (1936) published an early description of circulatory and visual effects of oxygen poisoning in man, and Donald (1947) later published a more comprehensive account of the nature and rate of development of neurologic symptoms produced in man by oxygen toxicity. The work of early German investigators on pressures ranging from hypobaric levels to several atmospheres of increased pressure, including a description of severe pulmonary oxygen poisoning in himself, was summarized by Becker-Freyseng (1950). Lambertsen and colleagues (1953) were the first to study critical questions of hyperoxic effects on oxygen and carbon dioxide transport across the brain, on cerebral circulation, and on cerebral metabolism in man.

Significant insight into a potential mechanism of oxygen poisoning was provided by the hypothesis of Gerschman et al. (1954) that toxic effects may be produced by active intermediates whose rate of formation is enhanced by increased oxygen tensions. The active radical hypothesis and many additional biochemical pathways by which oxygen poisoning may occur were examined critically by Haugaard (1968) in a comprehensive review, summarizing much of his own original work along with that of other investigators. His review is particularly valuable since it includes relevant studies of many investigators who did not work directly in the field of oxygen poisoning.

Using the electron microscope and precise morphometric techniques, Kistler et al. (1967) gave an excellent, quantitative description of structural damage caused by pulmonary oxygen poisoning in rats. In a comprehensive review, Clark and Lambertsen (1971) have discussed all aspects of pulmonary oxygen poisoning in man as well as in smaller animals. Their review emphasizes dose-response characteristics of pulmonary function impairment in man and summarizes the results of their original work in this area.

Recent significant progress in understanding potential mechanisms of oxygen poisoning was provided by Fridovich (1975) who pointed out the probable role of superoxide dismutases as biologic defenses against oxygen-induced production of superoxide anions and other active intermediates. There is increasing evidence that superoxide dismutases have an important role in protection against pulmonary oxygen poisoning.

OXYGEN TOXICITY

J. M. CLARK

The articles included in this section are reprinted by permission of their original publishers, as follows:

Becker-Freyseng H.: Physiological and pathophysiological effects of increased oxygen tension, in *German Aviation Medicine in World War II*, vol. I. US Air Force Sch of Aviation Med, 1950, pp. 493–514.

Bert P.: *Barometric Pressure; Researches in Experimental Physiology*, translated by MA Hitchcock and FA Hitchcock. Columbus OH, College Book Co, 1943, pp. 578–580; 709–754; 849–851. Republished, Undersea Med Soc, 1978.

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Fridovich I.: Superoxide dismutases. *Ann Rev Biochem* 1975; 44:147–159. Copyright 1975, Annual Reviews Inc.

Gerschman R., Gilbert D. L., Nye S. W., Dwyer P., Fenn W. O.: Oxygen poisoning and x-irradiation: a mechanism in common. *Science* 1954; 119:623–626. Copyright 1954, Am. Assoc for the Advancement of Science.

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Lambertsen C. J., Kough R. H., Cooper D. Y., Emmel G. L., Loeschcke H. H., Schmidt C. F.: Oxygen toxicity. Effects in man of oxygen inhalation at 1 and 3.5 atmospheres upon blood gas transport, cerebral circulation and cerebral metabolism. *J Appl Physiol* 1953; 5:471–486. Copyright 1953, Am. Physiological Soc.

Smith J. L.: The pathological effects due to increase of oxygen tension in the air breathed. *J Physiol* (London) 1899; 24:19–35.

Stadie W. C., Riggs B. C., Haugaard N.: Oxygen poisoning. *Am J Med Sci* 1944; 207:84–114. Copyright 1944, Charles B. Slack, Inc.

The following article is referenced in this section but appears in the section indicated in parentheses:

Behnke A. R., Forbes H. S., Motley E. P.: Circulatory and visual effects of oxygen at 3 atmospheres pressure. *Am J Physiol* 1936; 114:436–442. (Vision)

The following articles were recommended for this section by the compiler but could not be included due to length.

Bean J. W.: Effects of oxygen at high pressure. *Physiol Rev* 1945; 25:1–147.

Clark J. M., Lambertsen C. J.: Pulmonary oxygen toxicity: a review. Pharmacol Rev 1971; 23:37–133.

Dickens F.: The toxic effects of oxygen on brain metabolism and on tissue enzymes. *Biochem J* 1946; 40:145–186.

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Chapter V–E

PHYSIOLOGICAL AND PATHO-PHYSIOLOGICAL EFFECTS OF INCREASED OXYGEN TENSION

By HERMANN BECKER-FREYSENG

FORMULATION OF THE PROBLEM

The toxic effect of oxygen has been known since the classical investigations of Paul Bert (1873) and Lorrain Smith (1899). Since oxygen is used for so many technical and therapeutical purposes, their work has gained practical importance during recent decades. When the development of high altitude flying necessitated prolonged breathing of pure oxygen or of an oxygen-air mixture, aviation required that all questions concerning oxygen poisoning or the "upper critical oxygen tension" be answered. The following special problems arose:

Various scientists suggested that oxygen, if used long enough, might have a noxious effect under the conditions of high altitude. The well-known Italian high altitude record flier, Pezzi (1938), warned that breathing pure oxygen below 8,000 m. (26,200 ft.) would produce "inflammation and burns of the respiratory passages." Physicians were also cautious about it. Gillert (1933) says that possibly there is an upper time limit as yet unknown beyond which the high altitude flier, breathing oxygen, will encounter difficulty. Therefore, it was necessary to determine *whether the oxygen pressures employed at high altitude, if continued long enough, would actually produce the effects described by Paul Bert and Lorrain Smith.*

In this connection the question arose as to *whether, in the long run, the organism is absolutely unaffected by the lack of nitrogen which normally is always available.* This question is inherently associated with that of whether the noxious effect of oxygen depends on the *oxygen tension* alone or whether other factors participate in producing the toxic effect.

Because of the impetus of recent research concerning the central regulating function of *carbon dioxide*—with which, in the United States Henderson's and in Germany Rein's names are associated—its importance as a causative factor of altitude sickness was discussed anew. Although Mosso's views on the purely physical causes of the reduction of carbon dioxide were definitely disproved, new doubt arose as to whether oxygen deficiency alone could explain all the aspects of altitude sickness.

Doubt arose as to whether breathing of pure oxygen is an effective countermeasure. Regarding this theory, the last word has not yet been spoken (Rein, 1938). It was feared that individuals staying at 7,000 m. (23,000 ft.) for more than four hours would suffer prolonged injuries, even if pure oxygen from a reliable system were used.

At first, therefore, it had to be determined whether oxygen actually is only a "symptomatic therapy" of hypoxia, or *whether the breathing of pure oxygen enables fliers who are not adapted to high altitudes to remain at altitudes below about 9,000 m. (29,500 ft.) for very long periods without injury.* If, however, injury did occur under such conditions, it had to be determined whether the injury was caused by oxygen breathing, and how it was related to the phenomena described by Bert and Smith.

Apart from the practical problems, as regards the physiology and pathology of the oxygen supply, aeromedical research was interested in the question of the toxic effect of oxygen and in further clarification of the remarkable fact that this substance, most necessary for life, in sufficient quantity may be poisonous.

Clamann was the first German aeromedical researcher to study oxygen poisoning. He proceeded from the problem of whether prolonged oxygen breathing at high altitude is noxious or innoxious. In 1938, he carried out the first experiments in the decompression chamber of the *Luftfahrtmedizinisches Forschungsinstitut,* Berlin. Then, in 1938 and 1940 followed two decisive experiments by Clamann and Becker-Freyseng, using themselves as test subjects. In the following years numerous animal experiments supplemented this series. In the *Physiologisches Institut,* Göttingen, Heck and Loeschcke (1942) studied the effect of increased oxygen tension on respiratory regulation. In the *Institut für Flugmedizin* of the *Deutsche Versuchsanstalt für Luftfahrt (DVL),* Berlin-Adlershof, Schwepper (1943) studied the effect of oxygen breathing at high altitude on the alveolar carbon dioxide tension. In the *Institut für luftfahrtmedizinische Pathologie,* University of Freiburg, Liebegott (1941),

Pichotka (1941) and Kühn (1943) studied the problem of the morphology and morphogenesis of pulmonary changes caused by increased oxygen pressure. Lehmann and Graf (1942) (*Kaiser Wilhelm Institut für Arbeitsphysiologie*, Dortmund) investigated the problem of the effect of increased oxygen tension on efficiency. The effect on enzyme systems was studied by Seelkopf (1941) (*Institut für Luftfahrtmedizin*, Munich) and by Fahr (1941). Seelkopf and Von Werz (1944) investigated the acid-base balance in oxygen poisoning. Maréchaux (1943) of the *Luftfahrtmedizinisches Forschungsinstitut*, Berlin, carried out oxygen experiments on vagotomized animals.

Anthony and his collaborators (1938-41) made numerous observations of the changes in blood and circulation occurring when oxygen is breathed for a short time. My investigations, carried out in collaboration with Pichotka (Becker-Freyseng and Pichotka, 1944), also included the effect of toxic carbon dioxide pressures.

Since Lorrain Smith (1899), two types of oxygen poisoning have been discriminated:

1. Acute oxygen poisoning, first described by Bert, in which, at pressures above 3.5 atmospheres of absolute oxygen pressure, death with impressive "strychnine-like" convulsions occurred within a few hours.

2. The subacute type, observed by Smith, in which lower pressures are fatal within days, and in which pulmonary injury is concomitant. Hederer and André (1940) suggested that two terms be used, the "Paul-Bert effect" and the "Lorrain-Smith effect." These two terms will be used in the following discussion.

RESULTS

Effect on animals

The upper critical oxygen tension

Life is possible only within a limited range of oxygen tension. An oxygen tension of 30 mm. Hg is *the lower critical tension. The upper critical tension* will be understood as that tension above which, irrespective of the time of exposure, symptoms of oxygen poisoning will appear. Agreeing with the literature, table V-7 shows that this limit cannot be determined as precisely as can the lower critical oxygen tension. Although conclusive results cannot be expected from the small number of test animals, it is likely that the lowest oxygen tension used—474 mm. Hg in dry ambient air—has a different toxicity for different species. Guinea pigs seemed the most susceptible. At any rate, at 474 mm. Hg the upper critical oxygen tension has been exceeded, for all the animals of this experimental series showed at least transient disturbances. The limit of 60 percent oxygen at 760 mm. Hg barometric pressure (corresponding to 456 mm. Hg oxygen tension, dry), given in the literature (Binet and Bochet, 1938; Armstrong, 1938), was largely confirmed by my findings, although an exact tension limit cannot be given. Aside from *oxygen tension*, the toxic oxygen effect depends on the time of exposure. Table V-7 shows that increases in oxygen tensions are correlated with decreases in time of exposure. This ratio can be demonstrated roughly by a hyperbola. For obvious reasons, therefore, a concentration × time function must be assumed for the toxic effect of oxygen.

Hederer and André (1940), according to the formula $c \times t = constant$, derived a constant which applies only to pressures between 6 and 12 atmospheres absolute pressure of oxygen and which varies from 270 to 210 (!) even in this range. A preliminary calculation of all numerical data shows that *there is certainly no simple relationship between pressure and time*. Very probably in the above formula t must be provided with an exponent which varies with c, and secondly, the normal pressure $pO_2 = 150$ *mm. Hg*, at which under no circumstances toxic phenomena occur, must be considered.

My results also indicate to a certain extent that on one hand the tolerance to toxic oxygen pressures

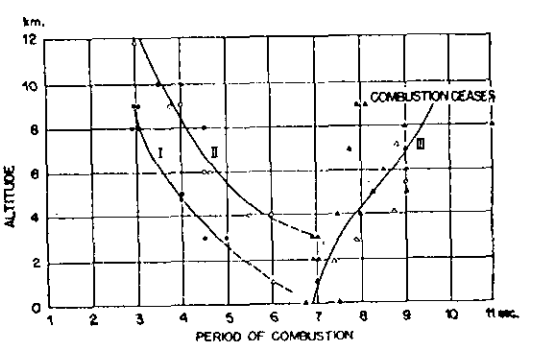

FIGURE V-66.—Combustion period of paper straps under reduced barometric pressure as related to the percentile oxygen content at constant partial pressure (I and II) and constant percentage of oxygen content at decreasing partial pressure (III).

• I. pO_2 = 150 mm. in the lungs.

○ II. pO_2 = 100 mm. in the lungs.

△ III. O_2 content 21%.

(According to Clamann, 1939.)

TABLE V-7.—*Summary of the animal experiments concerning the problem of toxic oxygen effect*

pO_2 ambient	Experimental condition	Test animal	Onset of the first symptom	Onset of death	Remarks
474 mm. Hg	3 ata* air	5 mice	*1010'* respiratory disturbance	14000'/24400'	3 survive.
		5 rats	*2400'* respiratory disturbance	14640'	4 survive.
		3 guinea pigs	*6750'* respiratory disturbance	9120'/11080'/19140'	
		2 rabbits	*6150'* respiratory disturbance		2 survive.
532 mm. Hg	1 ata air 70% O_2	12 guinea pigs	2520' and 4 cases after 2880' first respiratory disturbance. First respiratory convulsion after 5400'.	11280'-11580'/14460'/15960'	8 survive.
	1 ata air about 85% O_2; T = 19-21° C; F = 36-42.5%	18 mice	?	5760'/8640'	16 survive 168 hrs.
		10 rats	?		All of them survive.
		9 guinea pigs	2160' respiratory disturbance, want of appetite	4320'-4320'/5760'x 6/7200'.	
ca. 646 mm. Hg		8 rabbits	*2880'* dyspnea	5760'/7200'-7200'/8640'/8640'.	3 survive 168 hrs.
737 mm. Hg	T = 20°C; F = 80%; 1 ata air 97% O_2	6 rats	*1570'* unusual scratching, dyspnea	4260'/4860'/5460'/6240'/6600'.	1 survives for 75 hrs.
		4 guinea pigs	*1470'* orthopnea	4260'/5220'-7980'.	1 died after being taken out.
790 mm. Hg	5 ata air	10 rats	About *2040'* (?) orthopnea, probably observed too late.	3515'/3780'-4780'/4020'/4610'/4800'/4395'/5135'/5795'/5915'.	
		6 guinea pigs	About *3120'* (?) orthopnea	4595'/4775'-4850'-4895'-5100'-5160'	
790 mm. Hg	5 ata air	10 mice	*2280'* orthopnea (probably, it began much earlier).	2825'/3095'/3275'/3275'/6x3935'.	
1126 mm. Hg	7 ata air	18 mice	*375'* respiratory disturbance	2100'/2280'/2325'/2340'/2445'-10x 2760'.	3 survive 46 hrs.
		15 rats	*375'* respiratory disturbance	1890'/2085'/2085'/2205'/2205'/2400'/2445'/2520'/7x 2610'.	
		9 guinea pigs	*780'* respiratory disturbance	1320'-1560'/1890'-1965'/2205'/2280'/2325'/2400'.	1 killed.
1422 mm. Hg	9 ata air	3 mice	About *360'* first respiratory disturbances. *630'* first convulsions.	1350'/1520'	1 survives 20 min.
		3 rats	About *600'* (?) respiratory disturbances	1200'/1230'-1350'.	
		3 guinea pigs	About *360'* respiratory disturbances	930'/930'/1040'	
		2 rabbits	About *180'* respiratory changes	1350'/1500'.	
2280 mm. Hg	3 ata O_2	12 guinea pigs	35' convulsions, 40' respiratory disturbance. *115', 45', 55', 55', 50', 35', 30' convulsions*, 35'/30' respiratory disturbance, 45' respiratory disturbance (55' convulsions).	602'/720'/607'/723'	8 animals were observed only until the first symptom had occured.
		1 rabbit	75' convulsions	285'	
2660 mm. Hg	3.5 ata O_2	3 rabbits	105', 110' convulsions	180' 225' 360'	
3040 mm. Hg	4 ata O_2	6 guinea pigs	30', 20', 70', 100', 132', 170'	137', 446'	4 ditto.
		1 rabbit	100' convulsions	200'	
3560 mm. Hg	4.7 ata O_2	1 rabbit	35' convulsions	90'	
3800 mm. Hg	5 ata O_2	8 guinea pigs	13', 26', 27', 28', 55', 70', 70', 80' convulsions.	74', 139', 145', 164'	4 ditto.
		1 rabbit	25' convulsions	65'	

*Ata—absolute pressure in atmospheres.
54 mice, 59 rats, 72 guinea pigs, 19 rabbits.
The italic figures are average values.

shows considerable *individual variation*, and on the other hand that *additional factors*, such as the temperature and the humidity of the test room, the state of nutrition of the test animals, and the fluctuations of pN_2 associated with changes in pO_2, *play no decisive role*. The "biological insignificance" of atmospheric nitrogen for pulmonary respiration is in contrast to the important role that the nitrogen content of the air plays in combustion. The combustion rate (see fig. V-66) depends not only on the oxygen partial pressure but also on the volumetric portion in percent; *i.e.* on the ratio of oxygen to nitrogen (Clamann, 1939).

The methods used in my experiments will not be discussed here, since the most essential factors, particularly ventilation of the test chamber, mainte-

nance of the oxygen tension, etc., have already been described in published reports (Becker-Freyseng and Clamann, 1942). The experiments with total pressures of more than one atmosphere absolute pressure were carried out in a pressure chamber, which has the shape of a horizontal cylinder, 1 m. in diameter and 2 m. long (constructor: J. O. Zeuzem, Frankfurt-on-Main).

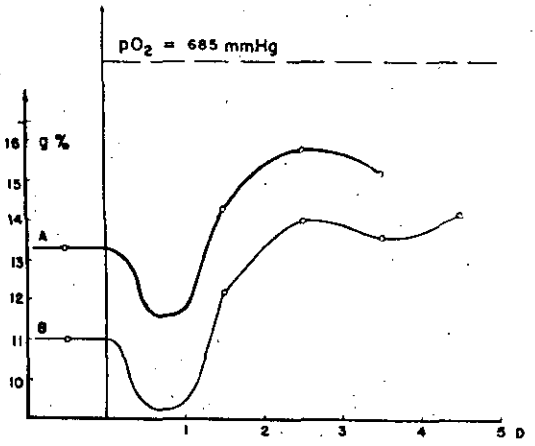

FIGURE V-67.—Hemoglobin values in two rabbits (grams percent). *Abscissa*: Time in days. Initial values in normal air. Pattern taken on the first day (according to Becker-Freyseng and Clamann).

Oxygen and carbon dioxide balance during inhalation of high oxygen and carbon dioxide partial pressures

The condition of poisoned animals often deteriorates rapidly when they are moved from the oxygen atmosphere into normal air. With progressive dyspnea, sometimes with convulsions, the animals die soon after they have been returned to normal air. Liebegott's (1941) and Pichotka's (1941) pathological findings indicate that because of exposure to increased oxygen tension, *diffusion is restricted* by a change in the barrier between alveolar air and blood. In addition to the early findings of pulmonary edema and bronchopneumonic areas, the Lorrain-Smith effect showed, as a characteristic finding, *peculiar broad bands, apparently homogeneous, attached to the alveolar and bronchial walls.* These were first thought to be *necrotic swellings of the alveolar membrane.* On the basis of later investigations, Pichotka no longer holds to this interpretation. He now thinks that these bands, *including their contents, are hyalinized capillaries.* It is further known that under high oxygen pressures the hemoglobin content of the blood changes. Figure V-67 shows the behavior of hemoglobin in two rabbits. Because of the investigations of other authors the changes within the first 24 hours did not have to be determined. After 24 hours the hemoglobin had already risen above its initial value, reaching its maximum after about 48 hours. According to present knowledge of the correlation between oxygen tension and hemoglobin content, this *increase of hemoglobin can only be considered the consequence of oxygen deficiency.* The arterial oxygen saturation which was observed in the same test series shows corresponding changes. Figure V-68 shows the findings in 27 rabbits. In this study, the total oxygen measured according to the method of Van Slyke was assumed to be oxyhemoglobin and was used as the basis for the calculation of the saturation. The oxygen in physical solution was intentionally disregarded. After a few hours of oxygen breathing the normal average 93 percent oxygen saturation fell and remained at an average of 83 percent provided oxygen breathing was continued for about five days. The arterial oxygen saturation of animals—which were returned to *normal atmospheric air* before blood samples were taken—decreased each day. On the fifth day three rabbits showed an oxygen saturation of 75.2, 54.1, and 50.9 percent respectively, in contrast to the initial values of 88.0, 99.0, and 93.5 percent.

The arterial blood of these animals was obtained by puncture of the left ventricle. Most of the ani-

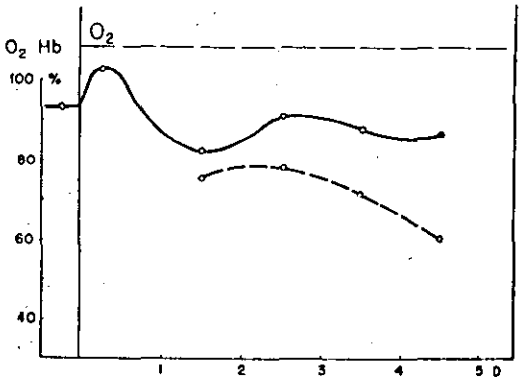

FIGURE V-68.—Arterial oxygen saturation during prolonged exposure to pure oxygen at normal barometric pressure. *Ordinate*: % O_2 Hb. *Abscissa*: Time in days. *Solid line*: Values in animals constantly breathing pure oxygen, *Broken line*: Values in animals returned to normal air shortly before blood samples were taken. Average of 27 rabbits (according to Becker-Freyseng and Clamann).

TABLE V-8.—*Oxygen tension in the tissue (mm. Hg) with an oxygen pressure in the ambient air of about 760 mm. Hg*

	Initial value	Value after: 9 hr. 30′	19 hr. 30′	31 hr. 30′	47 hr.	57 hr. 30′	67 hr. 30′	73 hr. 30′
Rabbit 18	37.2	93.5	112.1	80.4	45.2	41.0	35.5	25.2
Rabbit 30	33.9	49.5	56.1	47.7				

(According to unpublished experiments by Becker-Freyseng and Pichotka.)

mals survived four cardiac punctures on five successive days very well. Postmortem examination of the heart showed only the puncture point without any hemorrhage. In a few animals, however, the cardiac puncture led to a massive hemopericardium followed by a heart tamponade from which the animals died.

The assumption that there is a progressive oxygen deficiency has thus been confirmed. The organism tries to adapt itself to this hypoxia by increasing its hemoglobin, but finally it is unsuccessful. We understand that the animal's condition deteriorates rapidly when it is returned to normal air. In this phase of the Lorrain-Smith effect the increased oxygen tension plays a twofold role: It acts simultaneously as a *poison* and as a *therapeutic agent.* In this connection it is interesting to learn the behavior of the *oxygen tension in the tissues* (table V–8).

The determinations were made according to Campbell's (1924) well-known method of injecting an air bubble subcutaneously.

To understand the table it must be remembered that the tension of the carbon dioxide is balanced in the subcutaneous tissue after about 30 minutes. The oxygen equilibrium, however, is established only after a considerably longer time. Campbell states that it takes about 1½ to 3 days. The values of table V–8 must be studied with this limitation in mind. Although the absolute values do not correspond exactly to the actual conditions, they indicate with adequate certainty the direction which the course of the tension will take. For the first 24 hours the oxygen tension in the tissue increases. Later the tension falls and finally reaches subnormal values. *Summary: The Lorrain-Smith effect* involves a *temporary hyperoxia* for about the first 24 hours; *later* an *increasing oxygen deficiency* becomes evident.

In the Paul-Bert effect there is no oxygen deficiency prior to death (see table V–9). Considering the extremely long time required for the oxygen tension to reach equilibrium, it is clear that the actual oxygen tension in the tissue is considerably higher than the values obtained with Campbell's method.

As the injury is prolonged in the Smith effect, the carbon dioxide tension in the arterial blood rises (table V–10, Becker-Freyseng and Clamann, 1942).

TABLE V-9.—*Oxygen saturation, oxygen tension in the tissue, arterial carbon dioxide content and carbon dioxide tension in the tissue with oxygen tensions of 5 atmospheres absolute pressure*

Test animal	I % O_2-saturation		II pO_2 in the tissue		III Vol. % CO_2 arterial		IV pCO_2 in the tissue	
	Before	After	Before	After	Before	After	Before	After
Rabbit 24	92.3%	1 hr. at 5 atm. oxygen 93.2%.	20.0 mm. Hg.	1 hr. at 5 atm. oxygen, 287 mm. Hg.	42.0 vol. %	1 hr. at 5 atm. oxygen, 51.8 vol.%	46.4 mm. Hg.	1 hr. at 5 atm. oxygen, 161.3 mm. Hg.
Rabbit 2	95.2%	2 hrs. at 5 atm. oxygen 93.5%.	26.7 mm. Hg.	2 hrs. at 5 atm. oxygen, 330 mm. Hg.	30.2 vol. %	2 hrs. at 5 atm. oxygen, 44.3 vol. %.	48.2 mm. Hg.	2 hrs. at 5 atm. oxygen, 244.0 mm. Hg.

(According to unpublished experiments by Becker-Freyseng and Pichotka.)

TABLE V–10.—*Arterial CO_2 in vol. %*

	Initial value	First day	Second day	Third day	Fourth day	Fifth day
Rabbit No.:						
150	27.8	30.9	X 43.8			
701	31.2		X 37.0			
187	34.8		X 37.5			
847	36.8	35.5		X 32.1		
136	37.8		42.9	X 31.1		
705	53.4		51.6	X 33.5		
263	38.76	38.4				
226	31.7		46.0	32.1	X 19.5	
404	33.1			19.0	X 49.3	
192	37.2				51.6	
302	38.6		51.6		41.1	X 45.1
724	36.5			50.4	53.5	X 84.0
270	73.0				33.3	
174	30.6		49.3			
243	30.7			31.7		
17	42.2	39.9			36.1	
156	26.6		34.5			68.5
130	24.5			18.9	X 23.1	
147	42.2	47.5				
366	28.6					50.4
257	25.8			38.9		
167	34.2	36.5			54.5	
353	48.2					54.7
88	41.3					X 69.5

X = Blood samples taken after animals were returned to normal air.

Arterial carbon dioxide content in rabbits during prolonged exposure to an oxygen tension in the external air increased to 680 mm. Hg (according to unpublished experiments by Becker-Freyseng and Clamann).

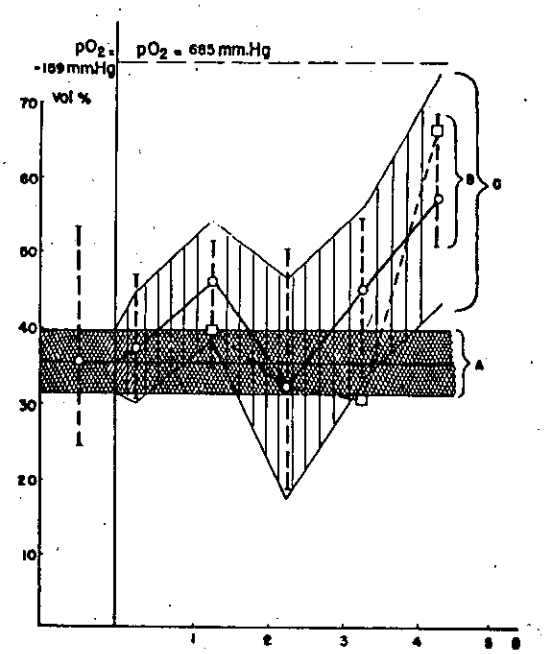

FIGURE V–69.—Behavior of the arterial CO_2 content of a rabbit breathing pure oxygen. *Ordinate*: CO_2 in Vol. %. *Abscissa*: Time in days. Average values of 27 test animals. *A* is the range of the triple mean error of the initial mean value; *C* is the range of the triple mean error of the respective diurnal values; *B* comprises the minimum to maximum values. o—o mean values; vertically broken lines: Minimum-maximum values; □ – – □ measurements after return to normal air (according to Becker-Freyseng and Clamann).

The marked increase among animals, which were returned to normal external air shortly before blood samples were taken, is striking. Figure V–69 includes the values of the arterial carbon dioxide tension: The increase on the fifth day is at least not an accidental phenomenon.

As the Smith effect continues the carbon dioxide tension in the tissue is markedly increased (table V–11) during the effective period of increased oxygen tension, on the average by 13 mm. Hg (Becker-Freyseng and Pichotka, 1944).

Seelkopf and Von Werz (1944) also measured the gas tensions in the tissue. They modified Campbell's original method in the following way: Thirty minutes before the experiment they gave guinea pigs an intraperitoneal, warmed injection of 6 to 8 cc. (depending on the weight) of sterile physiological salt solution with 6 percent gum arabic. At the end of the experiment this solution was removed by means of a trocar and syringe and analyzed according to the Van Slyke method.

TABLE V–11.—*Carbon dioxide tension (mm. Hg) in the tissue with an oxygen tension of about 760 mm. Hg in the ambient air*

	Initial value	Value after: 9 hr. 30′	19 hr. 30′	30 hr.	38 hr.	47 hr.	57 hr.	70 hr.
Rabbit 18	45.7	56.0	58.2		52.5	56.6	50.7	79.4
Rabbit 30	45.0	68.2	71.2	56.1		52.1	60.3	

(According to unpublished experiments by Becker-Freyseng and Pichotka.)

On the fifth and sixth days, at 1 atmosphere absolute oxygen pressure, they found increases of pCO_2 in the tissue which were greater than even those in the few cases I observed.

The maximum value which I and Pichotka (1944) found after 70 hours was 79.4 mm. Hg pCO_2. This agrees with the values which Seelkopf and Von Werz (1944) determined: 79.8 and 80 mm. Hg on the third and fourth days, respectively. The carbon dioxide tension, however, further increases and reaches 256.0 and 340.0 mm. Hg on the fifth and sixth days. These values were also found in the Paul-Bert effect.

On the other hand, it is significant that the slight rise in the carbon dioxide tension, which occurs during the first few days of the Lorrain-Smith effect, persists for a long time. This assumption, in turn, is supported by findings of Seelkopf and Von Werz. They found that in animals whose survival time was prolonged from 4 to 10 hours on the average after injection of magnesium oxide (see below), the carbon dioxide tension in the tissue averaged 143 mm. Hg in contrast to 201 mm. Hg in the control animals.

The *same behavior* of the arterial *carbon dioxide content* and of the *carbon dioxide tension* in the tissue is also found in the Paul-Bert effect (table V–9, columns III and IV). In the tissue the increase of the carbon dioxide tension is especially great.

According to my findings and those of Pichotka, Seelkopf and Von Werz, a *change in the alkali reserve*, which might have indicated shifts of fixed acids or of the alkali reserve between blood and cells, was *not* found. This applies to all types and phases of oxygen poisoning, so that increasing the *content or tension of carbon dioxide considerably* reduces the pH in blood and tissue.

A typical feature of the Paul-Bert effect and of the Lorrain-Smith effect is also the change in the respiratory rate. There is a decrease in the rate and terminal *gasping respiration* (fig. V–70). While in the Bert effect the course is a smooth one, the *rate* increases preterminally in the Smith effect, then proceeding to terminal bradypnea and gasping respiration. One is inclined to consider this the partially overlapping effect of different levels of carbon dioxide accumulation and of oxygen deficiency.

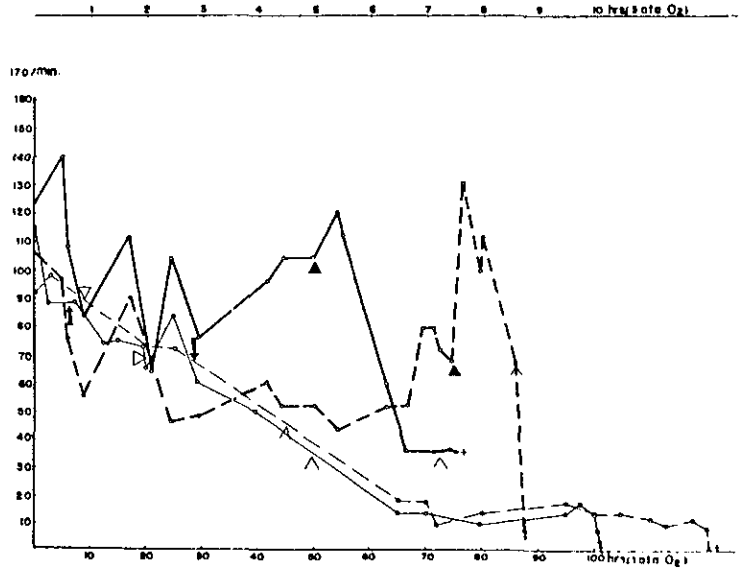

FIGURE V-70.- Respiratory rate of guinea pigs at various O_2-pressures. *Ordinate*: Respiratory rate per minute. *Abscissa*: Time in hours. The lower abscissa (0 to 100 hours) applies to the thick (solid and broken) curves. Upper abscissa (0 to 10 hours) applies to the thin curves. → first convulsion; △ first respirator disturbance; ▲ beginning of dyspnea; △ beginning of gasping respiration.

TABLE V–12.—*Oxygen and carbon dioxide tensions in tissue when there is increased carbon dioxide tension in the ambient air*

I	II	III	IV	V pO_2 tissues		VI pCO_2 tissues	
Test animal	pO_2 in chamber	pCO_2 in chamber	Duration of test	Before	After	Before	After
Rabbit 730	141 mm. Hg	239 mm. Hg	1 hr. 32'	33.2 mm. Hg	28.2 mm. Hg	39.8 mm. Hg	141.5 mm. Hg.
Rabbit 606	143 mm. Hg	253 mm. Hg	2 hrs. 42'	31.1 mm. Hg	21.6 mm. Hg	38.9 mm. Hg	232.5 mm. Hg.
Guinea pig 3	149 mm. Hg	213 mm. Hg	1 hr. 00'	20.0 mm. Hg	14.0 mm. Hg	49.0 mm. Hg	172.0 mm. Hg.
Guinea pig 22	158 mm. Hg	255 mm. Hg	2 hrs. 34'	19.0 mm. Hg	10.0 mm. Hg	51.6 mm. Hg	429.0 mm. Hg.
Guinea pig 25	154 mm. Hg	253 mm. Hg	0 hr. 51'	20.6 mm. Hg	15.7 mm. Hg	57.0 mm. Hg	238.0 mm. Hg.
Guinea pig 21	158 mm. Hg	255 mm. Hg	2 hrs. 33'			44.4 mm. Hg	162.7 mm. Hg.*
Guinea pig 16		220 mm. Hg	4 hrs. 7'			51.6 mm. Hg	278.0 mm. Hg.

*Measured 20' after death.

(According to unpublished experiments by Becker-Freyseng and Pichotka.)

According to these findings, *particular importance must be attached to the behavior of the carbon dioxide tension in oxygen poisoning.* The literature (Bean, 1931; Campbell, 1927, 1937; Behnke, Johnson, Poppen, and Motley, 1935) contains a great deal of evidence. Yet, the Paul-Bert effect has thus far usually been explained by the *carbon dioxide* theory. However, *the practically equal changes of carbon dioxide content and carbon dioxide tension in both the Paul-Bert effect and the Lorrain-Smith effect deserve particular emphasis.* The next step was, therefore, to study the immediate effect of increased carbon dioxide tension. Suggested by Pichotka, these experiments were carried out by the latter in cooperation with me in 1944.

The first orientation experiments showed a striking similarity between the clinical pictures of carbon dioxide and of oxygen poisoning. *All characteristic features of the Paul-Bert and of the Lorrain-Smith effects can be reproduced by adding carbon dioxide to the inhaled air.*

When an increased carbon dioxide tension is breathed, *the oxygen tension in the tissue* shows a marked *decrease* (table V–12). In this connection the delay in reaching equilibrium between the actual oxygen tension in the tissue and that in the artificially inserted air bubble must be remembered. The progress of the change (table V–12, column V), however, leaves no doubt that in the course of carbon dioxide poisoning the tissue lacks oxygen. This is easily understood in view of the *tremendous rise of the carbon dioxide tension* (table V–12, column VI) and of the mutual effect of both these gases on each other—the Bohr effect. The carbon dioxide content of the arterial blood (table V–13) rises distinctly. The increased carbon dioxide comprises that portion which develops in the tissue and that which diffuses along the new tension gradient from the ambient air into the body. At a 40-mm. Hg carbon dioxide tension (alkali reserve), the carbon dioxide content does not vary considerably. When the hemoglobin content in the arterial blood is constant, the arterial oxygen saturation and the arterial oxygen content fall parallel to the oxygen tension in the tissue (table V–13, column VIII)

TABLE V–13.—*Arterial carbon dioxide and oxygen contents, alkali reserve, hemoglobin content and oxygen saturation when the carbon dioxide tension in the ambient air is increased*

	I	II	III	IV		V		VI		VII		VIII	
				Vol. % CO_2		Alkali reserve (Vol. % CO_2 40 mm. Hg)		Vol. % O_2		% O_2 saturation		Gm. % Hb	
Test animals	pO_2 in chamber	pCO_2 in chamber	Duration of test	Before	After	Before	After	Before	After	Before	After	Before	After
Rabbit No. 606	143 mm. Hg.	253 mm. Hg.	2h 42'	40.1	83.5	43.1	39.0	14.5	9.6	80.6	61.3	13.4	11.7
Rabbit No. 730	141 mm. Hg	239 mm. Hg	1h 32'	42.9	66.9	46.4	48.0	14.9	14.3	87.4	77.7	12.7	13.7

(According to unpublished experiments by Becker-Freyseng and Pichotka.)

Summary: Corresponding to the clinical picture, the characteristic changes of the gas metabolism are found in both oxygen poisoning and primary carbon dioxide poisoning.

Respiratory regulation during exposure to high oxygen pressures

In protracted experiments with ourselves as test subjects, Clamann and I (1939) found that *the alveolar carbon dioxide tension falls when pure oxygen is breathed.* Heck and Loeschcke (1942) confirmed this finding and showed that the fall in alveolar carbon dioxide serves to regulate respiration and does not indicate reduced carbon dioxide production. This regulation aims at stabilizing the carbon dioxide tension in the tissue.

If the organism can stabilize the carbon dioxide tension from the oxygen dissolved in the plasma, a correspondingly smaller amount of the oxygen combined with hemoglobin will be consumed during exposure to increased oxygen tension. A correspondingly smaller amount of the reduced hemoglobin will be formed which is required for the transport of carbon dioxide from the tissue. Christiansen, Douglas, and Haldane (1914) showed the correlation between the absorption of carbon dioxide and the oxygen content of the blood. Because of this transport disturbance, the carbon dioxide increases in the tissue. By affecting the respiratory center, this rise increases the respiratory minute volume. Thus, the alveolar carbon dioxide tension is reduced and a new tension balance is established which effects the delivery of carbon dioxide from the tissue in a more satisfactory manner. Heck and Loeschcke were able to demonstrate in their test subjects the increase of the respiratory minute volume and the decrease of the carbon dioxide content of the arterial blood.

These results were confirmed by direct measurement of the gas tensions in the tissue (fig. V-71). When first starting to breathe oxygen, even an anesthetized test animal has an increasing respiratory minute volume and consequently a decreasing alveolar carbon dioxide tension and arterial carbon dioxide content. Thus, it is possible during the first few hours of exposure to oxygen to maintain the carbon dioxide tension of the tissue at a level which is scarcely above normal. On the other hand, since the alveolar carbon dioxide tension decreases, naturally the tensions of the other gases in the alveoli, including oxygen, increase in proportion to their percentile volume.

It must be possible to change the carbon dioxide tension in the tissue by eliminating these regulatory

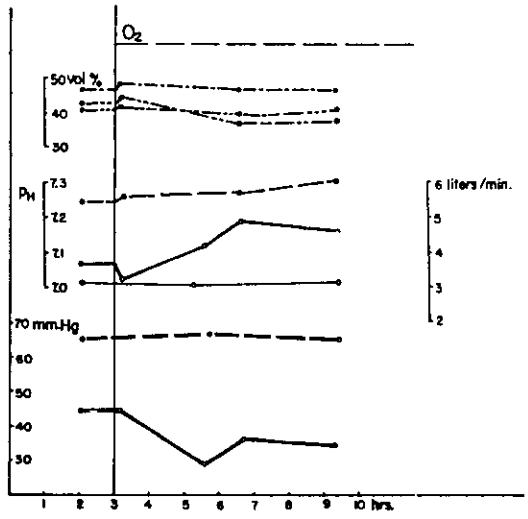

FIGURE V-71.—Respiratory regulation in a dog under morphine-urethane narcosis. After third hour pure oxygen with normal pressure is breathed through a tracheal cannula. ═══ pCO_2 in alveolar air; ——— pCO_2 in tissue; ——— respiratory minute volume; - - - - pH in tissue, - - - - - pH arterial; —— - —— venous CO_2 content; - — - — - — arterial CO_2 content; ——— alkali reserve (CO_2 content at pCO_2 = 40 mm. Hg).

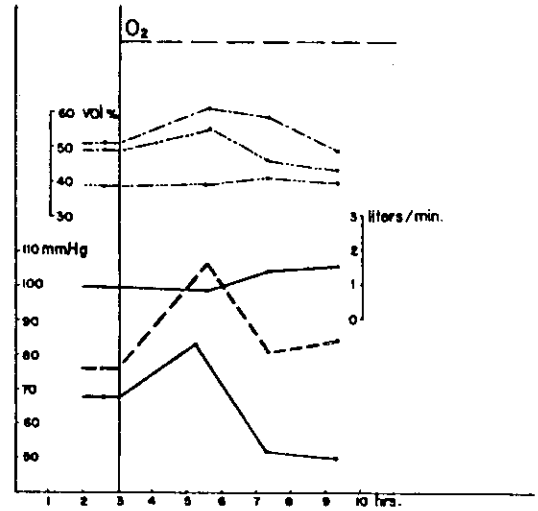

FIGURE V-72.—As in fig. V-71. Another test animal in deeper narcosis.

measures (fig. V–72). A very deep morphine-urethane narcosis so increased the threshold of excitability of the respiratory center in one test animal that during the first few hours of oxygen breathing the respiratory minute volume did not increase. *With the respiratory minute volume constant, the carbon dioxide tension increased* in tissue and in alveoli. When the respiratory center again became active as the effect of the narcotic wore off, the respiratory minute volume increased to about 150 percent of the initial value. At the same time the carbon dioxide tensions in the alveoli and in the tissue decreased.

Effect on man

It has been clear from the beginning that under flying conditions toxic phenomena, such as those of the Lorrain-Smith effect, occur only if oxygen is used for a very long time. Therefore, the oxygen tension or percentile volume was so chosen in these experiments that the experiments could be continued for several days.

The effect of prolonged oxygen breathing under increased tension (increased oxygen content at normal barometric pressure).

Clamann and I carried out this experiment on ourselves as subjects in the 40-m.³ decompression chamber of the *Luftfahrtmedizinisches Forschungsinstitut*, Berlin. As in the animal experiments, an air conditioning installation assured that temperature, moisture, and carbon dioxide content of the air remained normal. Although these factors are not decisively important in oxygen poisoning, their influence should be considered during prolonged experiments. During this experiment the oxygen content was raised to 90 percent on the average; the total pressure was equal to the normal barometric pressure—about 760 mm. Hg.

Nothing unusual occurred during the first 24 hours. After the second day my pulse rate and body temperature increased; there was a decrease in my vital capacity. Prickling and a numb sensation of the finger tips were experienced by Clamann at the end of the second test day, and also by me at the beginning of the third day. During the course of the experiment these paresthesias intensified in both of us, spreading from the middle fingers to all the other fingers. On the third day they also occurred in the toes. My vital capacity continued to decrease; my pulse and temperature increased; my general constitution was markedly affected. Transitory pains in both knee joints occurred. In the night preceding the fourth day; my vital capacity decreased to 60 percent of the initial value, and rate and depth of respiration increased. There was also a distressing subjective feeling of dyspnea. In the same night Clamann was awakened by severe cardiac palpitation. For about 10 minutes the pulse rate was 110 per minute; it gradually fell later. Clamann's vital capacity also fell. On the morning of the fourth day I noted sudden nausea and later vomited. Following this episode the experiment was discontinued after a total duration of 65 hours. Vomiting persisted for the whole day, recurring at intervals of about 1 hour. The pulse rate (at complete rest in the recumbent position) was 72 per minute, the axillary temperature was 37.5° C. The severe dyspnea associated with coughing and expectoration of thick mucus, the paresthesias, the vomiting recurring at intervals of 1 hour despite complete rest and abstinence from food, and the slight fever, were considered severe symptoms—particularly because of the obscureness of diagnosis and therapy. Therefore, I was hospitalized that night. The vomiting ceased without specific therapy. The paresthesias gradually disappeared in the course of the following 2 weeks. After about a week the pulmonary symptoms disappeared and I was dismissed from the hospital. However, the vital capacity did not reach its original value until after about 6 weeks. In Clamann no special symptoms occurred after the experiment was ended.

My blood count showed that on the second day the hemoglobin fell from 17.3 gm. percent to 16.2 gm. percent, rising again to 17.2 gm. percent on the third day. During these 3 days the erythrocyte counts were 5.5, 5.6, and 6.0 millions per mm.³ The leucocytes increased from 6,200 to 12,000 and to 12,700 per mm.³ Clamann's hemoglobin showed the same changes. It decreased from 17.1 gm. percent to 16.1 gm. percent on the second day, increasing to 17.2 gm. percent on the third day. The red counts were 5.6 and 5.7 millions per mm.³ on these 3 days.

Except for my last value the alveolar carbon dioxide tensions were greatly reduced below normal (table V–14). The same result was shown by a 12-hour experiment, using the same oxygen tension, which was carried out as a control for this striking finding.

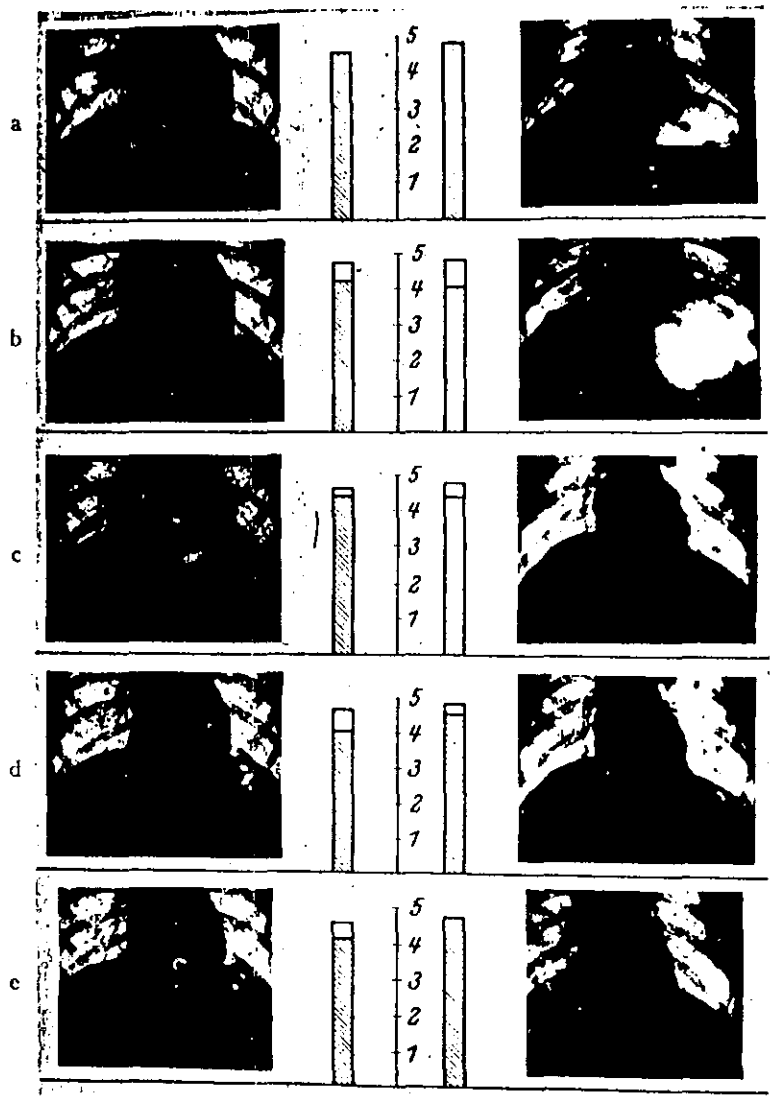

FIGURE V–73.—Position of diaphragm (X-ray photograph) and vital capacity (in liters) in two test subjects during a 70-hour experiment at 9,000 m. (29,500 ft.) altitude with 82% O_2. The white fields above the hatched columns of the vital capacity correspond to the deficit as compared to the initial value at zero meters.

(a) at ground level on first day of experiment
(b) at 9,000 m. on first day
(c) at 9,000 m. on second day
(d) at 9,000 m. on third day
(e) at 9,000 m. on fourth day

(After Becker-Freyseng and Clamann, 1942.)

TABLE V-14.—*Alveolar carbon dioxide tension (in mm. Hg) in man when the oxygen tension in the ambient air is increased to about 780 mm. Hg*

Test subject	Normal value	After 2 hr. 00′	After 18 hr. 10′	After 46 hr. 25′	After 64 hr. 00′
B.-F.	42.0	30.7	28.6	35.8	40.5
Cl.	40.0	31.5	33.6	30.7	32.6

[According to Becker-Freyseng and Clamann]

Effect of increased oxygen content in the inhaled air under decreased atmospheric pressure

The above experiment involves *conditions which do not exist in high altitude flying—i.e., increased oxygen tension with normal barometric pressure.* Therefore, it was necessary to carry out a similar experiment with the atmospheric pressure reduced as it is in high altitude flying. A simulated altitude of 9,000 m. (29,500 ft.) was chosen for the following reasons:

1. At 9,000 m., 82 percent oxygen content secures the same oxygen partial pressure as that which normally exists at sea level, *i.e.*, 150 mm. Hg.

2. At 9,000 m. there should be no decompression symptoms.

3. This altitude is similar enough to practical conditions for one to judge whether or not oxygen breathing alone is enough for the flier to remain at 7,000 to 10,000 m. (23,000 to 32,800 ft.) for an *infinite period* without injury.

The results of this experiment, carried out on both Clamann and myself, *proved that if the oxygen supply is reliable one can stay at 9,000 m. (29,500 ft.) for as long as 70 hours without injury.*

An unpleasant subjective phenomenon was flatulence. Strangely, this persisted during the whole experiment. In fact, all X-ray pictures (fig. V–73) show elevation of the diaphragm by the expansion of stomach and intestines. In Clamann the expansion of the stomach was initially more severe but it quickly receded during the experiment. The *changes in the vital capacity* might be attributed to this altitude meteorism which continued for 70 hours (fig. V–74). In Clamann the correlation between vital capacity, respiratory minute volume, alveolar carbon dioxide tension, and alkali reserve seems to be simple: Parallel to the onset of meteorism and the resulting elevation of the diaphragm, the vital capacity decreased, the respiratory minute volume increased, and the alveolar carbon dioxide tension fell, while the alkali reserve remained almost constant. At first, the foregoing conditions also applied to myself. However, whereas in the case of Clamann all values had returned to normal even before descent to sea level, my reduced vital capacity remained unchanged. Only the respiratory minute

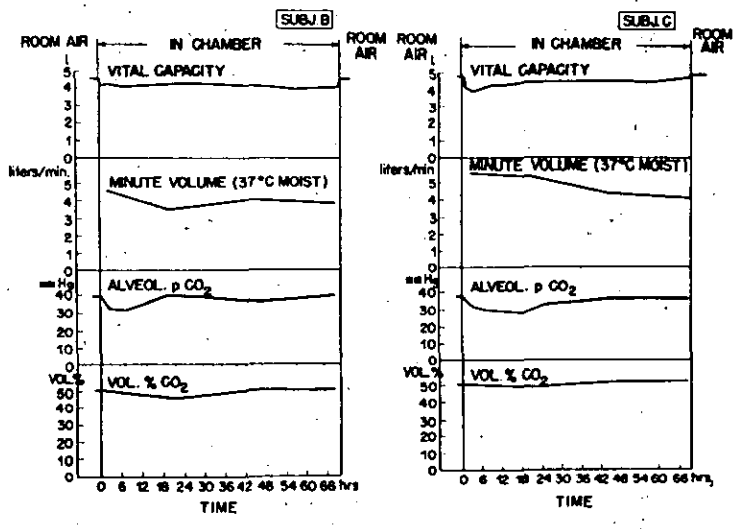

FIGURE V-74.—Vital capacity (in liters), respiratory minute volume, alveolar CO_2 tension, and alkali reserve under conditions equal to those of fig. V–73 (according to Becker-Freyseng and Clamann, 1942).

volume and the alveolar carbon dioxide tension were about normal. The alkali reserve varied within normal limits. The blood showed no uniform change.

If the oxygen supply is adequate, disturbances of the oxygen balance and of the carbon dioxide balance need not be anticipated even if the individual remains at 9,000 m. (29,500 ft.) for several days.

Decompression symptoms do not limit the period spent at an altitude of 9,000 m. (29,500 ft.).

Even after a long time *altitude meteorism* is not completely eliminated.

DISCUSSION AND CONCLUSIONS

The dependence of the toxic oxygen effect on the oxygen partial pressure

With the natural reservation that the time factor be considered, Paul Bert's statement made in 1873 is still valid: *La tension d'oxygène est tout* (The tension of the oxygen is all that matters).

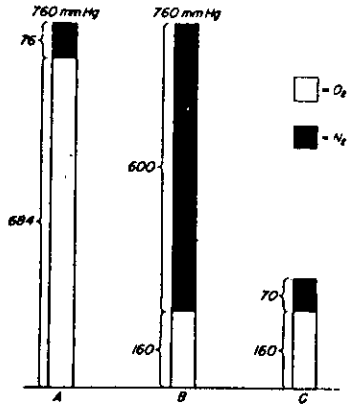

FIGURE V–75.—Ratio of oxygen partial pressure to nitrogen partial pressure with normal air at zero meters (column B); with 90% O_2 at zero meters (column A); and with an oxygen partial pressure of 160 mm. Hg at 9,000 m. (29,500 ft.) (column C) (according to Becker-Freyseng and Clamann, 1942).

According to animal experiments, the result is the same whether the increased oxygen tension is produced by *increasing the oxygen percentage* with *normal barometric pressure* or by *increasing the total atmospheric pressure with the oxygen percentage unchanged.* Both *result in an increased oxygen tension.* These experiments also show that except for oxygen no other factors need be considered and that nitrogen in particular has no effect. Figure V–75 shows which changes of the percentile nitrogen content and of its tension must be anticipated in the various experiments. Table V–15 compares the results of the various experiments on man, considering especially the percent contents and the tensions of oxygen and nitrogen.

The toxic effect of oxygen is specifically determined only by the oxygen tension. Figure V–76 shows the time elapsing before the onset of the first disturbances in man, as found by various authors. Since the agreement of these results with those of animal experiments is satisfactory, further conclusions as to the effect on man can be drawn from that on test animals.

Fortunately *the practical conclusions for aviation* from the above are very favorable. According to figure V–76, above an altitude of about 3,750 m. (12,300 ft.), the upper critical oxygen partial pressure will not be reached. *Also, with the longest probable duration of oxygen breathing at high altitudes, symptoms referable to oxygen poisoning should not be anticipated.* Moreover, on the basis of the second 70-hour experiment at 9,000 m. (29,500 ft.), I assume that oxygen breathing at high altitude is something more than just "symptomatic therapy."

The changes in the carbon dioxide balance, which are also observed when the oxygen supply is adequate at high altitudes, probably may be attributed to altitude meteorism (fig. V–77).

TABLE V–15.—*Effects of increased oxygen content on man as related to the atmospheric pressure*

Total pressure and altitude	O_2%	pO_2 alv.	N_2%	pN_2 alv.	Effect on man
	Referred to 21% O_2 at 760 mm. Hg		Referred to 79% N_2 at 760 mm. Hg		
760 mm. Hg = 0 m.	Increased (90%)	Increased (641 mm. Hg).	Decreased (10%).	Decreased (71 mm. Hg).	Ultimately noxious.
230 mm. Hg = 9000 m. (29,530 ft.)	Increased (82%).	Equal (150 mm. Hg) ...	Decreased (18%).	Decreased (32 mm. Hg)	Endurable throughout.

(According to Becker-Freyseng and Clamann.)

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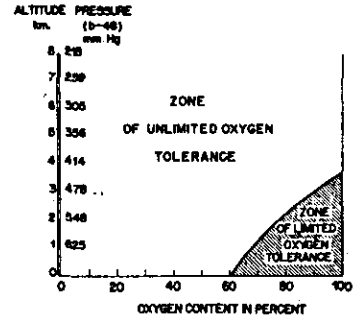

FIGURE V-76.—Oxygen tolerance in relation to altitude and oxygen content (%) on the basis of an "upper critical oxygen pressure" of 427 mm. Hg. In the lower right section the tolerance is additionally determined by the time factor (according to Becker-Freyseng and Clamann, 1942).

With increased oxygen tension and normal barometric pressure, the fact that the alveolar carbon dioxide tension decreases is probably a result of the regulative increase of the respiratory minute volume. At high altitude however (assuming equal production of carbon dioxide), the lowering of the alveolar carbon dioxide tension due to meteorism may be explained by one of the following causes: The respiratory center can be excited from the flatulent gastrointestinal canal or from the elevated diaphragm. Or, according to the premise supported by Rühl, Rückert, and Thaddea (1936), because of the elevation of the diaphragm, the resting respiratory level, the respiratory minute volume, and the alveolar carbon dioxide tension are changed. Schwepper (1943) also found a decrease of the alveolar carbon dioxide tension at 7,500 m. (24,600 ft.) when the oxygen supply was adequate. His lowest value is 31.8 mm. Hg. Schwepper assumes that the elevation of the diaphragm caused by altitude meteorism is soon eliminated by the passing of the intestinal gases, so that Rühl's definition of the relative hyperventilation *cannot be a correct explanation* of the change in the carbon dioxide tension at high altitude. However, the measurement of the vital capacity and the roentgenological studies of the expansion of intestinal gases carried out during my experiments, showed that even *after several days, the normal level of gas in the intestine is not reached*. This finding, therefore, explains the change in the alveolar carbon dioxide tension.

Besides, because of hyperventilation of psychic origin a carbon dioxide deficiency may occur in flying. This will not be discussed in this paper.

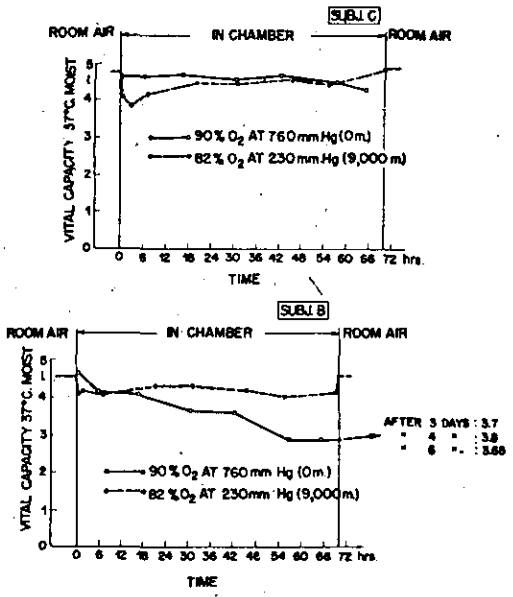

FIGURE V-77.—Behavior of vital capacity (in liters) at 760 mm. Hg barometric pressure and 90% oxygen, and at 230 mm. barometric pressure and 82% oxygen (according to Becker-Freyseng and Clamann, 1942).

The *fall of the alveolar carbon dioxide tension*, which was found to agree with the data of Talenti (1930), Jongbloed (1931), Winterstein (1934), and Rühl and collaborators (1936), *did not cause any injury even after 70 hours*.

Origin and nature of oxygen poisoning

In the beginning of this chapter the difference between the Paul-Bert effect and the Lorrain-Smith effect was pointed out. The essential features of each of these poisoning effects are generally characterized as follows: Convulsions are typical of the Paul-Bert effect, whereas respiratory disturbances are typical of the Lorrain-Smith effect. Hederer and André (1940) pointed out that, although such a discrimination is reasonable for practical purposes, it does not mean that there is a strict separation into two processes which are different in nature. I fully agree that *the two toxic effects occur simultaneously, varying only in intensity*. I was repeatedly convinced by my own experiments on guinea pigs that even in the Paul-Bert effect, under absolute pressures of 3, 4, and 5 atmospheres of pure oxygen, the first visible changes can be respiratory, preceding the convulsions by some time. Also, in

the Paul-Bert effect, no animal died without gasping respiration. On the other hand, the animals showed *definite disturbance of sensitivity in the Lorrain* Smith effect. Scratching and wiping of the mouth, which had not been observed with the same intensity and frequency, again and again indicated paresthesias. The latter were also observed in man showing the Lorrain-Smith effect. Hederer and André reported some findings which they considered specific for one of these effects. In their opinion only the Paul-Bert effect was reversible. I, myself, observed that under the conditions of the Lorrain-Smith effect severely injured animals were returned from the oxygen-rich atmosphere into normal air, surviving without symptoms. Vice versa, animals did not survive the Paul-Bert effect despite their being alive when returned to normal air. Survival does not depend on the previously effective oxygen tension but on the length of time which the animal has been exposed to a certain oxygen tension, or on the injury which has developed within this time. Likewise, Hederer and André state that only the poisoning in the Paul-Bert effect follows the law of mass effect. I think that both effects are subject to the same laws. The formula $P \times t = M$ set up by Hederer and André, however, does not include the whole range of tensions.

An important finding is the fall of *body temperature*. This, as well as the increase of carbon dioxide, was found in oxygen poisoning over the whole range of tensions. It was demonstrated in the Paul-Bert effect by its discoverer in 1873 and in the Lorrain-Smith effect by Hill and Macleod in 1903.

In my opinion, the Paul-Bert and the Lorrain-Smith effects can be considered the same. Both develop according to the same law. They have the same cause and change into each other easily.

The *oxygen balance*, however, is *different* in the *two forms of toxic effect*. The Paul-Bert effect is constant *hyperoxia*. Both the oxygen in solution in the blood and that in the tissue are increased, showing a tension higher than normal. The Bohr effect, which plays a role in carbon dioxide intoxication, is completely unimportant as compared with the oxygen tension which is increased by about 20 times in the Paul-Bert effect. In contrast hereto, the hyperoxic state in the Lorrain-Smith effect is only temporary and is followed by a phase of *oxygen deficiency*. The common genesis of both forms of toxic effect, therefore, cannot be based upon the behavior of oxygen in the organism. *Only carbon dioxide behaves the same in both cases.* The content and tension of carbon dioxide are increased in both forms of oxygen intoxication. Whereas an enormous increase of the carbon dioxide tension in the tissue occurs very rapidly in the Paul-Bert effect, it occurs rather slowly in the Lorrain-Smith effect. Accordingly, in the Paul-Bert effect all phenomena appear within a short time, and are very intense and distinct. The Lorrain-Smith effect, in which the carbon dioxide tension takes a longer time to rise and in which the effect lasts longer, shows the same phenomena in slow motion, partly indistinct and complicated by hypoxia. Especially convincing is the fact that the whole syndrome of oxygen poisoning can be reproduced by suddenly increasing the carbon dioxide tension in the inhaled air. Up to a certain point of the injury, carbon dioxide poisoning is as reversible as is oxygen poisoning. Seelkopf and Von Werz (1944) provided what may be considered evidence for the carbon dioxide theory of oxygen poisoning. They reasoned that, should this theory be true, the rate of carbon dioxide accumulation in the tissue must be reduced by the administration of alkali, thus delaying the onset of injury and of death. Therefore, they gave 125 mg./kg. magnesium oxide to their guinea pigs by means of a pharyngeal probe and found an average survival time of 10 hours as compared with the 4 hours of control animals.

The causal relationship between oxygen poisoning and impairment of the carbon dioxide balance also is indicated by the finding of Shaw *et al.* (1934). They observed that, if the oxygen tension and the carbon dioxide tension increase simultaneously, the symptoms of oxygen poisoning appear much sooner than when only the oxygen tension is changed.

According to recent studies, the early findings concerning the disturbances of the enzymes seem to be somewhat uncertain. Whereas according to reports of Lehmann (1935), Libbrecht and Massart (1937), Bohr and Bean (1940), it seemed as if certain enzymes, such as succino-dehydrogenases and cytochromes, were impaired or blocked in their oxidized phases by increased oxygen tension, Seelkopf's investigations (1944) showed that the extent of such enzyme inhibition is considerably smaller than has thus far been indicated. Seelkopf found

that neither cytochrome *c* nor the cytochrome oxidase is changed by oxygen; that lactic and succinic dehydrogenases are scarcely affected by pure oxygen at one atmosphere and only slightly at six atmospheres absolute pressure; and that, according to examinations of the pulmonary tissues of animals poisoned by oxygen, the dehydrogenases are slightly impaired only after a long exposure (at the end of the third day) to pure oxygen at 678 mm. Hg. Finally, Seelkopf investigated the carbonic anhydrase, after Orzechowski (1942) had stated, that he considered impairment of this enzyme by high oxygen tension possible. However, this view is also incorrect, as seen in figure V-78.

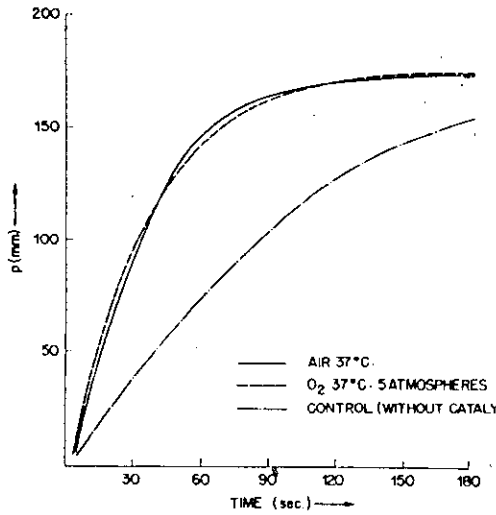

FIGURE V-78.—Effect of 5 atmospheres oxygen pressure on carbonic anhydrase (according to Seelkopf, 1944).

Seelkopf explained the positive findings of early authors in the following way. According to their experimental setup, the oxygen abundantly present in solution oxidizes the substrates, such as succinic acid, glucose, hexose monophosphate or hexose diphosphate, and lactic acid, in the initial phase of the experiment via the system of cytochrome oxidases, cytochromes, and dehydrogenases.

Thus even *before the beginning of the main experiment, part of the substrate is consumed;* therefore, it is the rate of decrease of the substrate's concentration, and *not the inactivation of the dehydrogenases, that is determined in the main experiment* under increasing oxygen pressure. Consequently, *a false experimental arrangement simulates the highly poisonous effect of oxygen on dehydrogenases and above all on the succinic dehydrogenases.*

As compared with Seelkopf's (1944) experiments, Fahr's (1941) results are hardly convincing as to the enzyme theory. Fahr states that after intraperitoneal injection of lactoflavin, nicotinamide or glutathione in guinea pigs, he observed fewer and weaker convulsions than in untreated control animals. In his experiments with five atmospheres absolute pressure of oxygen the first severe tonoclonic convulsions occurred after 10 to 20 minutes. According to my experiments (see table V-7), such short periods before onset of symptoms are rare. In guinea pigs the average time elapsing before the first convulsions was much longer. Besides, even under normal conditions the frequency and severity of the convulsive attacks differed so greatly that it is not possible to draw definite conclusions from "lighter" or "weaker" convulsions. On the other hand, even the greatest enzyme inhibition would not explain the essential symptom of oxygen poisoning—the increase of tissue carbon dioxide—for an enzyme inhibition would be associated with less carbon dioxide in hypoxidosis than under normal conditions. Accordingly, content and tension of carbon dioxide ought to decrease; actually, the reverse is the case.

It can only be said that neither pure *pressure effects* nor the effects of changes in the nitrogen balance have been proved to be causes of oxygen poisoning.

Since the processes are essentially the same, differentiation into a *compensation phase* and a *decompensation phase* seems to be more important than classification into acute and subacute oxygen poisoning or into the Paul-Bert and Lorrain-Smith effects. *Compensation counteracts the accumulation of carbon dioxide.* The importance of this compensation for carbon dioxide also is obvious from the fact that above the lower critical threshold the metabolism does not vary with the oxygen tension (Regnault and Reiset, 1849). The organism need not take any measures against the high oxygen tension and its direct effect on the cells. While in the *compensation* phase a number of *regulative* measures are recognized, *decompensation* is characterized by *pathological reactions* which are functional and morphological in nature.

Hyperoxic regulation: In 1857, Fernet had found that when the oxygen pressure is greater than normal the erythrocytes can hardly absorb more

oxygen than when their oxygen tension is balanced with that of normal ambient air at 760 mm. Hg barometric pressure. *In vitro*, at 160 mm. Hg oxygen tension the blood is fully saturated with oxygen. It was, therefore, the more astonishing that within 24 hours in the animal experiments with oxygen tensions of 600 to 700 mm. Hg, the saturation was not always complete. Recent investigations by Matthes, Queralto, and Malikiosis (1937) have shown that *in vivo* total saturation is reached only at about 300 mm. Hg oxygen tension and that at higher oxygen tensions in the alveolar air, the difference between alveolar and arterial oxygen tension increases. Whether this is to be considered a regulative measure cannot be decided from the findings so far obtained. On the other hand, the amount of oxygen which hemoglobin is able to absorb, in addition to that it contains at normal oxygen tensions, is small. The main importance must be attached to the oxygen in physical solution in blood; this was indicated by Bucquoy in 1861. If the oxygen tension increases by 1 mm. Hg, this oxygen in physical solution increases at 37° C. by 0.003 volumes percent.

In contrast to the combination of oxygen with hemoglobin, the physical solution of oxygen in the plasma is practically a linear function which, with a given temperature, depends on the oxygen pressure only. At pressures above about 10 atmospheres, Cassuto (1904) discovered extremely slight deviations from the linear course. Despite the extremely small absorption coefficient, the amount of oxygen absorbed at 3.6 atmospheres absolute pressure (2,653 mm. Hg alveolar oxygen tension with 40 mm. Hg pCO_2 and 47 mm. Hg pH_2O considered) is as much as 8.0 volumes percent (referred to 760 mm. Hg barometric pressure). This is just the amount of oxygen sufficient to balance the difference between arterial and venous oxygen saturation. This finding, which was also discussed by other authors, especially by Behnke and collaborators (1934–35) and by Hederer and André (1940), seems to be of decisive importance, for this is the oxygen tension at which the Paul-Bert effect and the Lorrain-Smith effect separate.

As is generally known, the reduction of hemoglobin is not only the basis for the gradients of oxygen tension and of diffusion required for the next arterialization, but also effects almost all of the transport of carbon dioxide in the venous blood by an associated exchange of ions.

According to the classical examinations of Christiansen, Douglas, and Haldane (1914), the variation of oxygen saturation changes the absorption of carbon dioxide and thus the transport of carbon dioxide from the tissues by the blood. The transport of carbon dioxide is maintained by all the above regulative respiratory changes, *i.e.*, increase of carbon dioxide tension in the tissues, increase of the respiratory minute volume, and decrease of the alveolar carbon dioxide tension, as was first shown by the investigations of Heck and Loeschcke (1942). Each regulative mechanism, including the one described in this paper, has an upper limit of effectiveness. At very high oxygen pressures it can no longer prevent the carbon dioxide tension in the tissue from increasing. There should be no doubt, however, that the respiratory changes occurring in the Paul-Bert effect also represent the attempt at such a regulation. Whereas the respiratory changes are supposed to serve only the transport of carbon dioxide, a series of circulatory changes are explained differently.

According to the investigations of Anthony and collaborators (1938 II), two minutes after the inhalation of pure oxygen under normal pressure is started, a reduction of the erythrocyte and of the hemoglobin occurs, which after 10 minutes amounts to about 5 percent. Anthony (1939) pointed out that on account of this decrease in hemoglobin the oxygen tension in the tissue is reduced by 2 mm. Hg. According to Anthony and Bechthold (1939), the diameter of the erythrocytes diminishes due to the increased power of oxyhemoglobin to bind alkali. Fifty minutes after the beginning of oxygen breathing, the erythrocytes and the hemoglobin have returned to their normal initial values. This concludes the first phase of the changes in the blood. The following second phase includes a prolonged and extensive reduction of the red blood components; this seems to have been observed first by Doyon and Morel in 1901. A more detailed analysis of these processes was made by Campbell (1927) and by Binet and collaborators (1938, 1939, 1941). In prolonged experiments on man, I was also able to demonstrate this "hyperoxic hypoglobulia" (Binet, Buchet, and Guiraud, 1939). Anthony's calculation, according to which a 30 percent reduction of the

hemoglobin is necessary to compensate the excessive oxygen in physical solution, is experimentally confirmed by the changes in this second phase. The third phase of the changes in the blood can no longer be considered a regulation and so will be discussed in connection with pathological symptoms.

Vascular changes due to increased oxygen tension were first demonstrated by Retzlaff in 1913. More recently, American authors (Lennox and Gibbs, 1932; Boothby, Lovelace, and Benson, 1940; Willmon and Behnke, 1941) demonstrated this vasoconstriction in various circulatory areas exposed to increased oxygen tension. In 1941 Anthony, Lent, and Müller, using Broemser and Ranke's method, found an increase of the peripheral vascular resistance and observed a decrease in the cardiac minute volume of about 15 percent, and in the heart rate of about 10 percent.

Anthony (1939) indicated that the changes in the blood components and in the physical circulatory values, in a sense, reduce or normalize the oxygen tension in the tissue. With the decrease of the cardiac minute volume the utilization of blood increases —*i.e.*, attempts are made to lower the venous oxygen tension. Thus the power of the venous blood to bind carbon dioxide improves. The increase of the intravenous oxygen tension, which is 12 mm. Hg with oxygen breathing under normal pressure and without regulation, is reduced by 50 percent during the temporary chemical and physical circulatory regulation.

Beneficial effects on the physical and mental efficiency could be observed only in this compensation phase. Thus, Lehmann and Graf (1942) investigated the effect of pure oxygen under normal pressure on the following activities: Algebraic problems in the form of addition and multiplication, the Bourdon test as modified by Baade, ciphering, cycling on a bicycle ergometer, and the hand-ergometer test. In most cases they found a distinct *increase of efficiency when oxygen was breathed*. The analysis of the working capacity shows that the increase of the oxygen tension in the blood stimulates cortical functions; this is manifested by an increase of will power. The increase of efficiency seems to be strictly limited to the time when oxygen is breathed. Whether this increase of efficiency is produced by the slight rise in the carbon dioxide tension, which increases the respiratory minute volume, is open to question.

Secondary concomitant phenomena are the changes in the electrocardiogram. These are prolonged diastole, prolonged conduction time, and elevated *T* wave (Anthony and Kümmel, 1939; Barach and Steiner, 1940). Nothing final can be said as to the origin of this circulatory regulation. In 1883 Lehmann discovered the direct effects of increased oxygen pressure on the cardiac muscles. Also, Bohr and Bean (1939) found in hyperoxia a decrease in frequency and intensity of ventricular contraction in isolated frog hearts. Also, the intestinal muscles react both to hyperoxia and to hypoxia with decreasing contraction frequency and loss of tonus (Bohr and Bean, 1940). The findings of Euler and Liljestrand (1942) show that in the living organism the reaction to increased oxygen tension does not come from the heart but from a superior regulation center. During oxygen breathing the pulse rate decreases when the carotid sinus is intact and increases when it is eliminated.

The interesting findings of Drastich (1925) may be mentioned as an example of a morphological regulation. Salamander larvae are able to vary the thickness of their bronchial epithelium directly with the oxygen tension of the water. At a low oxygen pressure it grows thinner by the reduction of cellular layers; at a high oxygen pressure it becomes thicker by increasing the layers and the individual structural elements. Accordingly, the conditions of diffusion of the respiratory gases change. Thus, assuming the structure of the protoplasm to be constant, carbon dioxide (with forty times the diffusion power of oxygen) is able to diffuse outward adequately, whereas the diffusion of oxygen is either facilitated or impeded. The findings of early American authors who observed in rats a correlation between the survival time and the thickness of the alveolar wall, are similar (Smith, Heim, Thomson, and Drinker, 1932).

All these regulations, however, are unable to overcome in the long run the noxious effect of increased oxygen tension.

Pathological reactions in hyperoxic conditions: The *increase of the carbon dioxide tension in the tissue is the* prominent feature of the noxious effect of increased oxygen tension in the *decompensation* phase. The increase of carbon dioxide tension

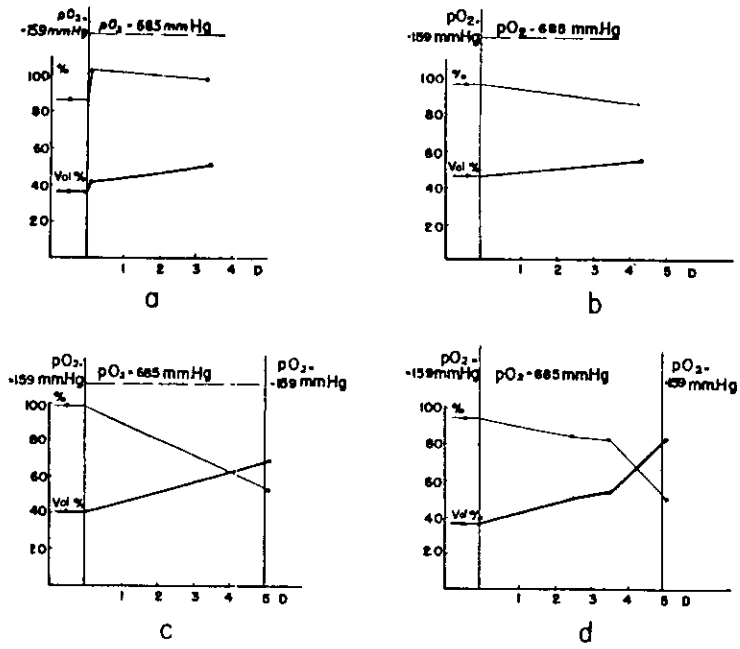

FIGURE V-79.—Behavior of the arterial CO_2 content (lower thick line) and of the arterial oxygen saturation in four rabbits (*a* through *d*) breathing pure oxygen at normal barometric pressure.

Ordinate: CO_2 vol. % and % O_2 saturation respectively; *abscissa*: time in days (according to Becker-Freyseng and Clamann; unpublished).

belongs to the syndrome of the Paul-Bert effect, because despite attempts at regulation it is impossible to transport all the accumulated carbon dioxide. In the Lorrain-Smith effect, however, the carbon dioxide increase is based on a different mechanism. From a larger series of similar findings, figure V–79 shows the almost inverse behavior of oxygen saturation and carbon dioxide content during a prolonged animal experiment under a 600 to 700 mm. Hg oxygen tension. Therefore, it must be assumed that the same pulmonary change that hampers the inward diffusion of oxygen also checks the delivery of carbon dioxide.

In the compensation phase, after an initial temporary decrease, the *hemoglobin* is again reduced by 30 percent for a longer period of time. *In the decompensation phase the normal value is finally reached once more and exceeded for the rest of the experiment* (fig. V-67). This constant increase of hemoglobin must be considered a reaction to the oxygen deficiency which in the meantime has set in.

As the Lorrain-Smith effect progresses further, the oxygen saturation constantly decreases. Even when there is an oxygen tension of 600 to 700 mm. Hg in the inspired air, the saturation is only about 80 percent. When the oxygen tension is that of the normal air—150 mm. Hg—the saturation continually decreases as oxygen poisoning progresses. The direct measurements in the arterial blood are confirmed by experimental pathological findings.

Liebegott (1941) was the first to find extensive changes in the papillary muscles and in the wall of the left ventricle of the rabbit's heart. These changes comprised the necrosis of whole areas of muscle fibers and their replacement by scar tissue. Electrocardiograms taken by Kühn (1943) proved the existence of hypoxic damage to the myocardium in guinea pigs. His examinations are especially convincing, since the changes in the ECG which occurred after the animals had been removed from oxygen into normal atmosphere (flattening of the

T wave, elevation or depression of the *S–T* segment, splintering and widening of the *QRS* complex, and extrasystole) disappeared after the animals had been returned to an atmosphere with *increased* oxygen tension.

In the course of the "decompensated" oxygen poisoning the "hyperoxic hypoxemia" is at first a surprise. Although Smith (1899) described an undersaturation of the arterial blood in some of his test animals, his finding never received any particular consideration. In the Paul-Bert effect hypoxia does not occur. It, therefore, cannot play a *decisive role* in the *fundamental* process of oxygen poisoning, but can only vary and complicate the Lorrain-Smith effect.

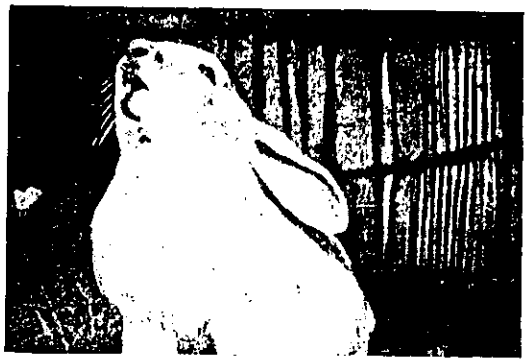

FIGURE V-80.—Rabbit at the end of the fifth day of the experiment, breathing pure oxygen under normal pressure and showing severe dyspnea and orthopnea (according to Clamann, Becker-Freyseng, and Liebegott, 1940).

In this connection, it must be considered that the increased carbon dioxide tension keeps the oxygen *pressure* high even when the oxygen *saturation* is low (Bohr effect). Seelkopf and Von Werz (1944) point out, therefore, that under these circumstances the significance of hypoxia should not be overestimated.

Hypoxia will have a certain effect upon respiration. Tachypnea (fig. V–70) and the typical orthopnea (fig. V–80) preceding the gasping respiration occur especially in the Lorrain-Smith effect. Both effects and the carbon dioxide poisoning, however, have in common the final atonic phase in which the four extremities are flaccid and the animal shows no movement except for gasping respiration (fig. V–81).

FIGURE V-81.—Rabbit about ten minutes after being removed from oxygen-rich atmosphere after seven days. Complete atonia; five minutes later, death occurred (according to Becker-Freyseng and Clamann, 1940).

Although after all, no doubt is left as to the causal importance of the increase of carbon dioxide tension in the tissue for oxygen poisoning in all phases, the only problem unsolved is the origin of the pulmonary changes. Morphogenetic research opens new fields of knowledge which will be discussed by Pichotka in the following chapter.

SUMMARY

1. An attempt is made to outline the nature of oxygen poisoning and its importance for aviation medicine.

2. Recent experiments are outlined whose results show that the different forms of oxygen poisoning (acute and subacute form, corresponding to Paul-Bert and Lorrain-Smith effects) must be considered the same. The common cause is the increase of the carbon dioxide tension in the tissue.

3. By increasing the carbon dioxide tension in the inhaled air it is possible to produce the same symptoms as those of oxygen poisoning.

4. The author's personal experiments concerning the tolerance of high percent oxygen content at various altitudes are described and conclusions are drawn for flying. The oxygen tension and the time of exposure are decisive for the toxic oxygen effect. Since the upper critical oxygen tension—about 425 mm. Hg—cannot be reached above an altitude of 3,750 m. (12,310 ft.), oxygen breathing at high altitudes is not limited by any time factor.

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BAROMETRIC PRESSURE

Researches In Experimental Physiology

BY

PAUL BERT

Translated from the French by

MARY ALICE HITCHCOCK, M.A.

Formerly Professor of Romance Languages at the University of Akron

and

FRED A. HITCHCOCK, Ph.D.

Associate Professor of Physiology at The Ohio State University

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Subchapter III

SUMMARY AND CONCLUSIONS

Summarizing, if we clear the principal results from the incidental questions which we have brought up and settled in the course of our research, the study of death in confined air under different pressures brings us to the following formulae.

In ordinary air:

A.—At pressures lower than one atmosphere, the death of animals occurs when the oxygen tension of the air is reduced to a certain constant value (which for sparrows equals on the average $O_2 \times P = 3.6$).

B.—For pressures included between 2 and 9 atmospheres, death occurs when the carbonic acid tension rises to a certain constant value (which for sparrows equals on the average $CO_2 \times P = 26$).

C.—For very high pressures, death is due exclusively to the too great tension of the ambient oxygen. It comes quickly when the tension of this gas reaches 300 or 400.

D.—For pressures of 1 to 2 atmospheres, death seems to be due especially to the lowering of the oxygen tension, but in part also to the rise of the CO_2 tension.

E.—Starting with 3 or 4 atmospheres, the fatal effect of the oxygen begins to be felt, and becomes very evident at about 9 or 10 atmospheres.

Experiments made either with gaseous mixtures more or less rich in oxygen, or in the presence of alkalis capable of absorbing the carbonic acid as it is formed, cause us to give to these laws an even greater character of generality, and we can formulate them in the following manner (applying them, for greater clearness, to sparrows):

The tension of a gas being represented by the product of its percentage multiplied by the barometric pressures, we see that death occurs:

A.—When the oxygen tension drops below 3.6, whether the barometric pressure is above or below the normal pressure; of course, in the first case, the carbonic acid must be removed by an alkali.

B.—When the carbonic acid tension rises above 26, whether the pressure is above or below the normal pressure; of course, in the latter case superoxygenated mixtures must be used.

What we say of carbonic acid is general for all *poisonous gases* (CO, HS, etc.); only the numerical value of the lethal tension will change. We shall return to this point when we speak of the hygiene of workmen in compression tubes.

C.—When the oxygen tension reaches about 300, whatever the percentage and the pressure are (the latter evidently cannot be lower than 3 atmospheres, with pure oxygen).

D.—These kinds of death can be combined by twos, A with B and B with C, according to the pressures and gaseous compositions used.

Death A is a real *asphyxia* for lack of oxygen; death B is a *poisoning by carbonic acid;* death C can be called, for convenience and in spite of the strangeness of the expression, a *poisoning by oxygen.*

We see—and this is the most general result reached—that in all cases the barometric pressure in its variations is never directly, of itself, the cause of the phenomena. It is only one of the conditions which alter the tension of the gases, and the other factor, the percentage, can completely offset its effects, if its progress is in the other direction, just as it will increase them rapidly, if its progress is in the same direction.

If now we leave out the carbonic acid produced, to place ourselves in conditions nearer those in which our present problem appears in nature or industry, setting aside certain phenomena which are quite secondary and to which we shall return at the appropriate time, we reach these conclusions:

1. That three animals, the first of which exhausts by its respiration a closed space full of air, the second of which is compelled to breathe in a current of air of diminishing oxygen content, the third of which is subjected to a gradual decrease of pressure, are all three, by these different procedures, threatened by the same symptoms and the same death, a death from lack of oxygen, a real asphyxia;

2. That two animals, one of which breathes in a current of air of increasing oxygen content while the other is subjected to a barometric pressure increasing from 1 to 5 atmospheres, are in identical conditions. That, besides, the animal which breathes pure oxygen at 2, 3, 4 atmospheres, etc., is in the same conditions as the one which breathes pure air at 10, 15, 20 atmospheres; both are, by these different procedures, threatened by the same symptoms and the same death, a death from excess of oxygen, a poisoning of a sort hitherto unknown.

All the influence which barometric modifications exercise on

animals is summed up in these terms: too low an oxygen tension or too high an oxygen tension.

Such is the very simple explanation given us by experiments in which we considered the ambient medium much more than the animal. But this too low or too high tension of the oxygen must be studied now, not only in its measure, but in its immediate consequences; the animal itself must also be examined with more care.

The first question which I shall now consider is that of the composition of the gases contained in the blood of animals subjected to different pressures.

[1] See my *Lecons sur la physiologie comparée de la respiration.* Lessons XXVII and XXVIII, p. 498-526. Paris, 1870.
[2] *Lecons sur les effets des substances toxiques et médicamenteuses.* Paris, 1857, p. 125.
[3] *Lecons sur les substances toxiques,* p. 140.
[4] *Lecons sur la physiologie de la respiration,* p. 517.

Chapter IV

ACTION OF COMPRESSED AIR ON ANIMALS

Subchapter I

TOXIC ACTION OF OXYGEN AT HIGH TENSION

The experiments reported in Chapter I, Subchapter II, have brought us to this remarkable conclusion, that compressed air, or, to speak more exactly, the oxygen which has reached a certain tension constitutes a dangerous element, often even fatal, for animal life.

This unexpected revelation, which is deduced from all our series of experiments in such a way as to be convincing to the most suspicious mind, deserved deep study. The symptoms of this unknown sort of poisoning in its different degrees had to be analyzed; the concentrations at which oxygen becomes dangerous had to be determined, both as to its tension in the exterior respiratory medium and as to its proportion in the interior respiratory medium, the blood; an explanation had to be found for its inner mode of action upon the different anatomical elements.

This new problem left far behind it in scientific interest the analysis of some modifications in the respiratory and circulatory rhythms hitherto studied by the authors who gave their attention to compressed air. I devoted myself to it at the very beginning with all the concentration of which I was capable. Having demonstrated successively that compressed air acts only by the tension of the oxygen which it contains, and that this oxygen can kill animals rapidly with convulsive symptoms, following the usual

method of physiologists, I had to set aside for the moment the effects of low concentrations of oxygen, which are hard to estimate, and study first the violent symptoms caused by high concentrations. In the first place, I investigated the action of oxygen under high tension, generally adding to the manometric pressure a percentage of oxygen sufficient to produce a value much greater than that in the air which we breathe.

I think it advisable to report here a certain number of experiments which will permit me to give first a description of the symptoms resulting from what I shall call, if only for convenience in nomenclature, *poisoning by oxygen.*

Already we have noted the convulsions which had attacked sparrows subjected to this dangerous agent. The following experiments, almost all performed in the Seltzer water apparatus, will furnish us new examples.

Experiment CCLVIII. January 29. House sparrow subjected to 6 atmospheres, 5 of which were oxygen, from 3:50 to 3:58. The mixture contained 81 per cent of oxygen, and the tension of this gas was therefore equivalent to $81 \times 6 = 486$, which corresponds to $\frac{486}{20.9} = 23.2$ atmospheres of air.

At 4:03, violent convulsions, the head hanging down; whirling.

I lower the pressure and bring it to 3.5 atmospheres. During the decompression, new convulsions.

Immediately after, third attack; then new attacks, weaker and weaker, at 4:06, 4:11, 4:14.

During the attacks, and in the intervals, the respirations are very deep and very hasty; the beak is wide open.

The attacks come oftener at intervals of 1 to 2 minutes, becoming weaker and weaker. They subside about 4:40; the bird remains lying on its back, its respirations become rarer and rarer, and cease at 5 o'clock, without any other movement.

At 5:10, the rectal temperature is 24°.

Experiment CCLIX. February 2. House sparrow, subjected to 6 atmospheres, 5 of which are oxygen. The oxygen tension is about 450.

After 5 minutes, strange tremors, a quivering through the whole body; then it remains motionless, its beak down.

After 10 minutes, an attack of strong convulsions; another at 12 minutes; a third, weaker, at 17 minutes. The bird is very sick, breathes from 50 to 70 times a minute, its beak wide open.

Brought back carefully to normal pressure; recovers a very little; rectal temperature, 34° to 35°. In its cage it has new convulsive attacks; at the end of a quarter of an hour, gets up on its feet; but when it is threatened with the finger, it draws back walking on the whole tarsus, and falls backwards.

After 2 or 3 hours, seems fairly well recovered, but dies in the night.

Experiment CCLX. February 5. Sparrow subjected to 5 atmospheres, 4 of which are oxygen. The oxygen tension is about 400. After about 15 minutes, strong convulsions occur; I allow 2 or 3 attacks, then restore normal pressure.

The rectal temperature is 32°.

The bird has evidently retained all its intelligence; it pecks viciously when a finger is presented to it, and uses its wings and feet strongly.

One hour afterwards, its temperature is 34°. It has had more of the slight convulsive attacks, and cannot keep on its feet.

3 hours afterwards, its rectal temperature has risen to 39.5°. Survives.

Experiment CCLXI. February 26. Sparrow; rectal temperature 40.5°.

Subjected to 5 atmospheres, 4 of which are oxygen (tension of about 400).

At the end of 5 minutes, beginning of uneasiness. I restore normal pressure rapidly by the capillary cock.

The temperature is 40.3°, but it rises rapidly to 40.5° after respiration in the air. The bird is very vigorous and very vicious. Red cranial suffusions, in abundant spots.

The bird walks, runs, climbs about the cage, but does not fly. If it is tossed into the air, it has great difficulty in flying and soon falls; it then refuses to fly up from the ground.

Survives; the next day, it flies very well; the suffusions persist for several days.

Experiment CCLXII. March 2. Sparrow at 5 atmospheres, 4 of which are oxygen.

After 5 or 7 minutes, convulsions begin; at the first appearance, I open the little cock. The rectal temperature rises to 41°, but very slowly after 38°.

Small bloody suffusions.

Experiment CCLXIII. May 23. At 4 o'clock, sparrow taken to 5 atmospheres, 4 of which are oxygen. Tension about 400.

After 15 minutes, slight convulsions; at 20 minutes, severe convulsions, two or three attacks. At 30 minutes, taken out.

Rectal temperature, 33°.

At 5:45, rectal temperature, 35°; still trembling, quite sick.

At 7 o'clock, dead; muscular contractions singularly slow.

Experiment CCLXIV. February 12. Sparrow; cylindrical apparatus.

At normal pressure, respiratory rate, 135. Raised to 3 atmospheres of air, respiratory rate, 115.

At 4:20, I pass a current of oxygen into the apparatus, and raise the pressure to 2 superoxygenated atmospheres.

At 4:30, new ventilation, and pressure raised to 3 atmospheres.

At 4:40, the same; pressure at 4 atmospheres.

At 4:55, the same, 5¼ atmospheres; little convulsions begin to appear.

At 5:06, new ventilation carried to 6 atmospheres. Convulsions return, in spasms.

Dead about 6:50.

The air then contained 73 per cent of oxygen and 0.5 per cent of carbonic acid.

The oxygen tension P x O_2 = 438 corresponds to 21 atmospheres of air.

Blood very red in the jugular. Bloody suffusions extending over the whole cranium.

Experiment CCLXV. March 29. Sparrow placed in the small Seltzer water apparatus.

At 2:50 we begin to compress oxygen up to 8 atmospheres; the capillary cock being open, the compression maintained is carried on in a current of air delivering more than a liter per minute.

At 3:15 great convulsions occur; I allow two attacks to succeed each other, at three minutes interval. Then, rapid decompression. The bird pecks the finger which I offer it, and appears intelligent.

Its rectal temperature is 32°. When out of the apparatus, it has a third attack, and dies at 3:22. The blood of the jugular vein is dark and contains no free gases.

Experiment CCLXVI. July 9. Sparrow taken to 7 atmospheres of superoxygenated air.

After 10 minutes, seized by tonic convulsions. Taken out after 15 minutes; the convulsions continue, or rather the bird is in constant opisthotonos. From time to time, the stiffness increases; the bird cries out, spreads its wings, and wraps itself in them; the tail feathers are spread out. Remains sensitive and appears intelligent. The attacks of rigor are some of them spontaneous, others clearly provokable by stimuli.

It dies 20 minutes afterwards.

Experiment CCLXVII. July 18. Sparrow taken to 5 atmospheres of superoxygenated air.

After 5 minutes, vomits, and appears in very bad shape. But the convulsions do not come until about 20 minutes after, and they are violent.

Taken out 5 minutes afterwards, it continues to have convulsions and stiffness with opisthotonos. Pecks the finger presented to it. Its rectal temperature is 37°.

Two hours after, is perfectly recovered; its temperature has risen to 41°.

Experiment CCLXVIII. May 24, 1874. Experiment made before a Committee of the Academy of Sciences.

Sparrow taken to 6 atmospheres, superoxygenated. It is 4 o'clock.

After about 15 minutes, slight convulsions occur, soon followed by severe attacks.

The bird is removed; it has large ecchymoses on the cranium. Its rectal temperature is only 30°.

Remains very sick and dies in the night.

The data which have just been given permit us from now on to describe the violent symptoms due to compressed air, to too high oxygen tension, and to prepare the physiological analysis of this poisoning.

The first question which we should ask ourselves is as follows: at what oxygen tension do the convulsive symptoms appear? Let us collect in a table (Table XIV) the experiments of Chapter I and those which precede.

Table XIV

1	2	3	4	5	6
Experiment Numbers	Barometric Pressure atm.	Oxygen tension (round numbers)	Equivalent in atmospheres of air atm.	Rectal Temperature	Symptoms and observations
CXXXIX	1.75	150	7	——	No convulsions
CXXXVIII	3	260	13	——	Id.
CXLI	4	300	15	——	Convulsions.
CXX	20	abt. 420	20	——	Convulsions; the apparatus leaks.
CCLX	5	id.	abt. 21	32°	Convulsions; withdrawn, survives.
CCLXI	5	id.	id.	40.2°	Withdrawn after first conv., survives
CCLXII	5	id.	id.	38°	Id.
CCLXVII	5	id.	id.	37°	Id.
CCLXIII	5	id.	id.	33°	Conv.; withdrawn after 30 min., dies.
CXXXVII	5	id.	id.	18°	Violent conv., dies in 25 minutes.
CXLII	8.5	430	21.5	——	Id.; dies in 20 min.
CCLXIV	6	440	22	——	Id.
CXLV	5.5	460	23	27°	Id.; dies in 20 min.
CCLXVIII	6	———	———	30°	Id.; dies during the night.
CCLVIII	6	480	24	——	Id.; dies.
CCLIX	6	id. (?)	id. (?)	35°	Id.; withdrawn; dies during night
CCLXV	8	———	———	32°	Id.; withdrawn; dies at once

We see from an examination of this table that the convulsions begin to appear with an oxygen tension expressed by the figure 300, which, if we used pure air, would correspond to about 15 atmospheres.

The harmful effects were observed much sooner, as graph A of Figure 22 shows, which expresses the proportion of oxygen remaining in the compressed air in which the birds died, when we took care to eliminate the carbonic acid formed. The harmful effects are very clear beginning with 6 and especially with 12 atmospheres.

But the convulsions appear surely only between 15 and 20 atmospheres. Experiment CXX, in which a linnet was taken to 20 atmospheres of air, shows their appearance; only they were

considerably weaker than those obtained with superoxygenated air. Furthermore, in Experiment CXXXIII, in which the pressure was 17 atmospheres, there were no convulsions. This apparent contradiction is explained by the simultaneous influence of the carbonic acid produced, which, being stored in the organism, plays a very pronounced anesthetic part there, as we shall see in a special chapter. Now we shall show in a moment that anesthetics stop or hinder the convulsions due to oxygen.

Let us give now a brief description of these convulsions; we shall have to return to them when we have studied them in dogs.

These convulsions occur at the end of a variable time, generally from 5 to 10 minutes; the bird shakes its head and feet as if it were walking on hot coals. There are strange tremblings, quiverings through the whole body. Soon, in more serious cases, it half-opens its wings, moves them quickly, and falling on its back, it whirls rapidly in the receiver, beating the air with its wings violently, its feet curled up against its belly; these phenomena last for a few minutes, then grow calm, then reappear in attacks which are more and more frequent and less and less strong until death. During the attacks, and in the intervals, the respirations are very deep and very hasty; the beak is very wide open. At very high pressures, death comes at the first attack.

These remarkable symptoms continue to appear after the bird, removed from the influence of oxygen, has been restored to the open air under normal pressure; they may even then end in death.

These attacks are often very clearly provokable, like those of strychnine (See Experiment CCLXVI); their general appearance recalls at the same time the irregular quiverings of poisoning by phenol,[1] and the tonic and clonic convulsions of convulsive strychnine attacks.

Neither sensitivity nor intelligence seems affected; the bird, taken from the receiver, looks at and tries to peck the finger which threatens it; it closes its eyelids when some object approaches its eye.

General locomotion is evidently much affected, besides the convulsive attacks, of course; the bird has ataxic movements; in certain cases, it can hardly stand on its feet; in others, it can walk, but not fly.

Finally—and this is the most important point of this research, after the observations of these symptoms—the inner temperature drops in all cases rapidly and considerably. It falls 10 and 15 degrees; I call particular attention to Experiment CCLV, in which,

although the temperature had fallen to 32° in less than a half-hour, it rose rather quickly to nearly 40° and the bird survived.

I shall later dwell upon this remarkable fact, to which at present I merely call attention; it shows very clearly that the symptoms of oxygen poisoning are not due to an exaggerated activity imparted to the intra-organic combustions.

The first idea which would come to mind, and I admit freely that it came to mine immediately, is that under the influence of this super-saturation of oxygen the animal tissues would be consumed excessively, that an increase in the temperature would result, and that the convulsions which appeared could be compared to those which precede the death of animals over-heated in a drying-oven. Now we can state immediately that this is not true, although later I shall analyze this important phenomenon thoroughly.

Finally I shall say a few words of a symptom always present in birds in cases of oxygen poisoning, a symptom which I have designated by the expression "bloody suffusions of the cranium." They are hemorrhages which fill the cranial diploe; in the mildest cases they consist only of very small dots; these dots are replaced by wide spots which become confluent in severe cases, and the spongy tissue of the bone fills with blood. They always begin in the occipital, but may affect the whole cranium. They appear before the convulsions, and when the bird does not die, they are not absorbed for several weeks. Although they always exist when the symptoms due to oxygen become serious, they are not especially characteristic of this poisoning. Since my attention was called to their existence, I have found them quite often in asphyxia and death by decompression. In fact, they were noted in some of the experiments reported in Chapter I; when they are not mentioned, it simply means that no one looked for them. I should add that I never saw them so extensive or so deep as in oxygen poisoning. I have no understanding of their mechanism; they appear without any convulsive phenomenon, and autopsies have not shown any apoplexies in any other part of the body.

Let us now analyze a little more deeply the phenomena just described. Upon what anatomical element does excessive oxygen act? What is the cause of the convulsions? Is the heart directly attacked, as it is by such a great number of poisons? The data which have just been reported would be insufficient to permit us to reply completely to these different questions.

We have had to use the best physiological reagent, the frog.

Experiment CCLXIX. February 27. Frog subjected at 2 o'clock to 7 atmospheres, 6 of which were oxygen. The oxygen tension corresponds to 505. In the evening, at 7 o'clock, nothing particular; seems a little uneasy.

February 28, at 9 o'clock in the morning, dead. No reflex actions of any sort; the motor nerves and the muscles are excitable. The heart, of a fine carmine red, beats slowly when exposed. Free gases in the blood.

The lethal air contains no trace of carbonic acid.

Experiment CCLXX. March 4. Frog subjected at 4 o'clock to 5 atmospheres, 4 of which were oxygen; the tension of this gas is about 300.

At 10 o'clock in the evening, swollen.

On March 5, at 2 o'clock, seems dead. The heart no longer beats spontaneously, but is excitable; the motor nerves and the muscles are excitable. By cutting through the spinal cord in the back, movements in the lower limbs are caused.

Experiment CCLXXI. February 29. Frog subjected at 6 o'clock to 4 atmospheres, 3 of which were oxygen.

The tension of this gas is 254.

The next day, March 1, at 3 o'clock, it is rigid and swollen, seems to have convulsive movements when one raps on the table. At 7 o'clock in the evening, is much weaker.

March 2, at 1 o'clock, dead, stiff. The heart beats, the nerves and the members are excitable; no movement is produced when the spinal cord is cut.

The lethal air contains no trace of carbonic acid.

Experiment CCLXXII. April 18. Frog subjected at 6 o'clock in the evening to 4½ atmospheres of superoxygenated air. The oxygen tension is represented by 335. Temperature 15°.

The next day, nothing especial in the appearance of the frog.

April 20, found dead at 1 o'clock. The heart, very pink, is still beating a little. The muscles are perfectly contractile.

Experiment CCLXXIII. June 17. Frog subjected at 4:30 to a pressure of 5 superoxygenated atmospheres. The heart is laid bare, temperature 20°.

June 18, at 11 o'clock in the morning, very weak, prostrated. No respiratory movements. Pulsations of the ventricles, rare, irregular; but the auricles alone beat 40 times per minute.

At 3 o'clock, decompression. A few weak heart beats yet. There are no reflex acts, but the motor nerves and the muscles are quite excitable.

Sugar in the liver, in a rather large quantity.

We conclude from all these experiments that oxygen does not kill by acting on the heart, the motor nerves, or the muscles. But

the reflex acts of the spinal cord, after being considerably excited, are checked.

The fact that the convulsions come from the spinal cord, communicating its excitation to the muscles by means of the motor nerves, is abundantly proved by experiments in which the motor nerve has been cut: Example:

Experiment CCLXXIV. June 20: Frog; *left sciatic nerve cut.*

3 o'clock in the afternoon; subjected to 3 superoxygenated atmospheres, containing 60.5 per cent of oxygen, 3 x 60.5 = 181.5 = 9 atmospheres of air.

Respiration ceases for a moment.

June 21. Respirations very rare; eyes protruding with widely rounded pupils; frog is swollen, rather weak; no convulsions.

June 22. 11 o'clock in the morning. No respiration; weak; eyes closed by the transparent lid. Clonic convulsions beginning in the right front leg, then becoming generalized, except in the *left hind foot;* then general stiffness; then weakness.

These attacks are excitable at will, by shock; but the frog soon seems insensible, as if dead.

Sudden decompression; no effect. In the outer air, does not breathe; the heart, exposed, beats 50 times per minute; the blood, which was red at first, grows progressively darker.

After about a quarter hour, excitation brings on new convulsive attacks, like the preceding. On exciting the right hind foot, movements of the right front leg are produced, but not of the left.

Frequently fibrillary contractions, in the muscles of the chest especially and also in the limbs, except the left hind foot.

During the convulsions, the heart does not seem altered.

Dies about 2 o'clock.

So section of a motor nerve prevented all convulsive movement, fibrillary or generalized, from appearing in the corresponding muscles.

Since oxygen injures the spinal cord, like strychnine, phenol, etc., convulsions should be prevented by chloroform, which, as I have shown before,[2] acts particularly on the spinal cord. In fact, this very thing happened in the following experiment.

Experiment CCLXXV. February 26. Etherized sparrow, put into the receiver; rouses during the compression. I put some drops of ether into the vessel in which the oxygen sucked in by the pump is bubbling in the potash, and raise the pressure to 5 atmospheres, 4 of which are oxygen.

The bird becomes unconscious again, after some quiverings of the feet; he dies slowly, in 25 minutes, *without any convulsion.*

Huge cranial suffusions.

The lethal air contains CO, 2; O_2 76. The original pressure of the oxygen was therefore about 78 x 5 = 390, corresponding to 19 atmospheres of air.

This experiment shows not only that anesthesia prevents convulsions from oxygen, like those of other poisons of the spinal cord, but also that it does not prevent death from coming, although it comes calmly. The following experiment, in which the animal was removed after the action of the oxygen, its convulsions appearing gradually as consciousness returned, is still more convincing.

Experiment CCLXXVI. February 24. Chloroformed rat, nearly died during anesthesia.

Begins to be sensitive, after about a half-hour. Rectal temperature 35°.

Subjected to 5 atmospheres, and after 10 minutes to 6½ atmospheres of oxygen.

At the end of 20 minutes of compression seems very sick; a few slight quiverings; the convulsions not appearing, it is withdrawn.

Rectal temperature 34°.

Put back into the cage, remains stretched out; it is soon seized by convulsions; stiffening of the tail, etc. They appear spontaneously or as soon as the animal is touched.

One hour after, same condition; temperature 32°.

2½ hours after, very slight convulsions; temperature 28°. Evidently dying.

February 25. Found dead and cold.

I do not dwell upon this point, because the experiments made on dogs will give us analogous data.

Before coming to the experiments on dogs, I think I should report one more which was performed on sparrows, and in which we see demonstrated the important part played by the blood in oxygen poisoning.

Experiment CCLXXVII. July 17. Two sparrows are subjected, from 5:02 to 5:07, to 8 atmospheres of superoxygenated air, in which the oxygen tension is equivalent to 424, that is, 20 atmospheres of air.

One, A, is in good shape; the other, B, which weighs 20 gm., was bled at 4 o'clock of 0.7 cc. of blood from the jugular; it is still very weak; its rectal temperature is only 32°, while A's is 42°.

At 5:10 or 5:12, A shows slight convulsive shivers, and about 5:20 real convulsions, which last until 5:33, when he dies. B is not affected until 5:25 and then slightly; no general quiverings, but great efforts in breathing, stiffness, etc., which become true convulsions, of the feet, if not of the wings, about 5:35; he has a few of them, then remains on his back as if dead.

Decompression at 5:45.

A, rectal temperature 31°.

B, rectal temperature 28°.

Enormous cranial suffusions on the two birds.

B is still breathing; his rectal temperature drops and is 25° at 6

o'clock; he dies then. When the muscles were pinched, they contracted slowly and strongly as if with cramps.

So in the animal which had been bled the symptoms appeared much more slowly than in the healthy animal. That is the effect both of the general weakening he had undergone and of the diminished quantity of blood, which, since it contained a smaller quantity of oxygen, could carry this dangerous agent to the spinal cord only in smaller proportion.

It would be premature to dwell at this moment on the part played by the blood in oxygen poisoning. This question will recur in a much more significant manner when we have studied the experiments made on dogs, which I shall now report in detail

When I used dogs as experimental animals, my special purpose was to investigate the proportion of oxygen contained in the blood when the convulsive symptoms occurred. I intended also to continue at the same time, thanks to the use of superoxygenated compressed atmospheres, the research of the proportions established in the living animal between the tension of the oxygen in the respiratory medium and the oxygen content of the arterial blood, proportions studied in Subchapter III of Chapter I up to 10 atmospheres of air only.

The experimental animal was fastened on his board as is explained in the subchapter just mentioned. To succeed in making him breathe compressed oxygen, I had recourse to a special device, not having at my disposal the quantity of oxygen necessary to compress this gas to several atmospheres in a receiver of 150 liters capacity.

I fixed in the dog's trachea a metallic tube as wide as possible, and connected it with a rubber bag having a capacity of about 30 liters. This bag was placed beside the animal, and the air injected into the chamber by the pump compressed both the oxygen and the animal at the same time. The experiment never lasted long enough for the dog to exhaust the oxygen entirely. But as the expirations were made into the bag, carbonic acid was stored up there, which consequently accumulated also in the blood. And so we should not take account of the proportion of this gas shown by the analyses; I thought, however, that I should indicate it as a matter of information in the account of the experiments. In a certain number of cases, to avoid this accumulation, I attached to the tube which went from the trachea to the bag, a flask in which the superoxygenated air bubbled in a solution of potash; in other cases, the solution was in the bag itself. These experiments,

compared to those in which no such precaution had been taken, allow me to state that in the latter the influence of the carbonic acid was quite negligible; that will be explained naturally, when we discuss poisoning by carbonic acid in Chapter VIII.

Here now is the report of a certain number of experiments.

Experiment CCLXXVIII. November 16. Black dog, short-haired, new subject, weighing about 12 kilograms.

It is fastened on its back, and in its trachea is inserted a metal tube, at the end of which is a rubber tube considerably narrower. Respiration is carried on in series of extreme frequency, separated by a few intervals of calm.

At the end of about a half-hour, the rectal temperature is 36° (in a healthy dog the same thermometer gives 38.5°).

Then from the left carotid 35 cc. of blood is drawn, which is immediately taken to the pump for extracting gases . . . . A

The dog is next placed in the compression apparatus; to the tube in its trachea is then fitted a rubber bag containing oxygen; then the animal is fastened as explained above.

Pressure is begun at 3:56.

At 4:21, the pressure is 5 atmospheres; I draw 38 cc. of very red blood, not letting gas escape . . . . B

At 4:40, at 7 atmospheres, drew 31 cc. of very red blood, in which escape of gas is at least doubtful C

Pressure is raised to 8 atmospheres, and at 4:45 decompression is made suddenly in 3½ minutes.

The animal is immediately withdrawn from the apparatus; there are no free gases in either the arterial or the venous blood; the heart sounds are normal, without any gurgling indicating the presence of gas. The rectal temperature is 30°. There has been an evacuation of fecal matter, and the mouth is full of froth.

The paws are much stiffened; when the animal is unfastened, he is in very pronounced opisthotonos; the whole body is in tonic convulsion. Fecal matter continues to be discharged. The eye closes when the cornea, but not when the conjunctiva, is touched; the pupils, much dilated, do not contract in light.

The arterial pressure in the carotid varies between 9 and 12 centimeters.

The symptoms continue to increase in intensity. About 5 o'clock, the convulsions are extremely violent; in the midst of continuous stiffenings, there appear clonic convulsions of the limbs, the neck, and the jaws. The eyes are convulsed. The penis is so retracted that to catheterize the animal the prepuce has to be slit its whole length; no urine in the bladder. The animal froths terribly.

About 5:30, the temperature is 29 degrees. Vomiting begins. The convulsions appear like fits, with no real rest in the interval; it appears much like successive strychnine attacks, except for the almost complete permanency of the stiffenings and the opisthotonos. Clonic convulsions are caused by touching the animal, by hitting the table,

by inserting the thermometer into the depths of the rectum. During the attacks, the respiration stops, but the heart continues to beat.

Gradually intervals of comparative repose appear. The animal begins to grind its teeth with such extraordinary force that one would expect them to break. The temperature rises again; at 6 o'clock it is 31°.

6:15; now and then, the stiffness disappears; the respiration is better; the tail moves.

6:45; the animal is still lying on its side; the clonic convulsions are like those of phenol, in that they almost imitate the motions of walking; they follow each other in attacks separated by an interval of relative repose. At each attack, violent opisthotonos, with quivering of the jaws, then a snapping of the teeth; from time to time, general stiffening with motionlessness, the stiffening less than at the beginning. The pupils are still insensitive to light. The temperature is 32 degrees. The heart beats hard and fast.

The next day, at 11 o'clock in the morning, the animal, in whose trachea the cannula has been left, is lying as on the day before; it is in opisthotonos with permanent contractions of the limbs; the anal sphincter is closed; weak, but almost continuous quiverings. Viscous salivation, as well as watering of the eyes, has continued; the pupils are dilated; the cornea is sensitive, but not the conjunctiva. Respiration quite calm; pulse 80, weak; temperature 27°.

I administered chloroform until the cornea lost sensitivity; the stiffening and quivering disappear to reappear soon.

The animal dies during the day.

Now here is the result of the analyses:

A: Ordinary air, normal pressure; 100 cc. of blood contain O_2 15.5 cc.; CO_2 22.9.

B: 5 *atmospheres of superoxygenated* air: 100 cc. of blood contain O_2 24.0; CO_2 63.

C: 7 atmospheres of superoxygenated air: 100 cc. of blood contain O_2 31.5; CO_2 54.6.

The air of the bag, after the experiment, contained per 100, O_2 66; CO_2 5.4. The original composition was therefore about 75 per cent of oxygen.

The oxygen tension in B was about $70 \times 5 = 350$.

In C, it was about $68 \times 7 = 476$.

It was raised to $66 \times 8 = 528$, which corresponds to about 26 atmospheres of air.

This experiment is particularly remarkable; here is an animal which, after being exposed for three-quarters of an hour to an oxygen tension corresponding to nearly 26 atmospheres of air, died after about 24 hours of violent convulsions.

Experiment CCLXXIX. November 20. Rather young dog, weighing about 8 kilograms.

Tube placed in the trachea.

After a quarter of an hour, the rectal temperature is 39.4°; pulse

144, respiratory rate 24; blood pressure in the carotid varies between 15 and 17 cm. of mercury.

At 3:38, drew 38 cc. of blood . . . . A

Placed in the apparatus at 4:10, with a bag full of a mixture with 89.5 per cent of oxygen.

At 4:30, pressure is 5 atmospheres, maintained there.

At 4:38, drew 43 cc. of very red blood; no gas escapes . . . . B

At 4:40, decompression in 1½ minutes.

The animal is immediately withdrawn, the bag is removed, and it is noted that it has already vomited in the apparatus. It vomits again. It shows attacks of stiffening without clonic jerks. The temperature is 36.5°; the arterial pressure from 11 to 12 cm.; pulse is 140, respiratory rate 24.

These attacks of convulsive stiffening last about 20 minutes.

At 6 o'clock, the temperature is 35°, the arterial pressure 12 cm., the pulse 140. The dog begins to be able to stand on its feet.

At 6:30, the animal, whose cannula has been removed, remains lying down with a sort of muscular trembling, resembling that of phenol poisoning. Its eyes are sensitive, and the pupils contract and dilate as if by tremors which are related to the quivering of the limbs. There are occasional stiffenings of the front feet, but they can easily be bent.

The next day, in good health.

The analyses gave the following results:

A: Air, normal pressure; 100 cc. of blood contain: O, 17.0; CO, 39.0.

B: 5 atmospheres of superoxygenated air: 100 cc. of blood contain: O_2 24.8; CO_2 75.0.

The gas in the bag after the experiment contains 76.2 of oxygen and 8.1 of carbonic acid. The oxygen tension in B was then about $77 \times 5 = 385$.

Experiment CCLXXX. November 25. Dog of average size.

Tube in the trachea; left carotid exposed.

Rectal temperature 38.1°.

3:12; drew 33 cc. of blood; the animal breathes quietly . . . . A

Placed in the apparatus at 3:55, with oxygen bag; between the bag and the tube in the trachea a flask is placed, at the bottom of which are bits of potash; by this means I intend to diminish the proportion of carbonic acid stored in the bag.

4:25; pressure 7 atmospheres; at 4:28, with great difficulty drew 23 cc. of blood . . . . B

4:38, pressure 7¼ atmospheres; sudden decompression.

Withdrawn at 4:45, the animal's eyes are sensitive; its temperature is 36°; there are stiffenings of the hind legs and the neck; the respiration seems suspended, the heart beats very feebly.

After 10 minutes the stiffenings increase, but the respiration returns, and the heart beats more quickly and strongly. Soon after, the animal again becomes limp, as it was when it was taken from the apparatus; its respiration is weak; it dies at 5:50, without moving.

At 5:20, its temperature was 34.5°; at 5:50, it had fallen to 33.5°.

At 5:05, I drew 33 cc. of blood from the carotid C

At 5:30, drew 33 cc. of blood also from the carotid . . . . D

The autopsy shows the heart full of dark blood on the right, a little red on the left. There are in the bladder some *drops of urine with an exceedingly high sugar content.* The liver contains much sugar.

Blood A (air, normal pressure) contained . . O_2 14.4; CO_2 41.0

Blood B (oxygen, 7 atmospheres) contained . . O_2 24.1; CO_2 68.5

Blood C (air, normal pressure, 40 min. after decompression) contained . . O_2 15.8; CO_2 16.5

Blood D (air, 70 min. after decompression) contained O_2 15.8; CO_2 28.3

The gas in the bag contained before the experiment 79 per cent of oxygen; the oxygen tension in B was probably 74 x 7 = 518; it rose to a maximum of 550 at 4:38.

Experiment CCLXXXI. November 27. Shepherd dog, weighing 16 kilos.

Tube in the trachea; rectal temperature 38.5°.

At 4:50, drew 33 cc. of blood from the left carotid . . . . . A

Placed at 5:08 in the compression apparatus with the oxygen bag, without the potash flask.

At 5:12, pressure is 1¾ atmospheres; drew 33 cc. of blood, very red. . . . . B

At 5:48, 7 atmospheres; this pressure maintained, and at 5:50, drew 39 cc. of very red blood, without free gases. C

At 5:53, decompressed in 2 minutes.

Withdrawn; temperature 38.5°. Is stiffened, and every three or four minutes, enormous tonic convulsion, with very violent opisthotonos, suspension of respiration, the heart continuing to beat, although more slowly. The eye lacks sensitivity. The excitability is much less evident than in strychnine poisoning. There are 4 or 5 of these frightful convulsions during which it seems as if the animal is going to fall from the table.

At 6:10, I administer to the dog a mixture of chloroform and ether; at the beginning, it seems as if the convulsions grow worse. But at the end of 2 or 3 minutes they disappear, and there are only quiverings of the front legs, like those caused by phenol, which disappear in their turn, as does the stiffening; the animal becomes relaxed and calm.

6:15, the anesthetic withdrawn. Sensitivity returns, then some fits of stiffening; but there are no more great convulsions. Temperature 39°.

6:22; drew 33 cc. of blood, medium red. . . . . D

6:45; the temperature is 38.5°.

7 o'clock; drew 33 cc. of blood, very dark. . . . . E

The next day, the animal is quite recovered.

Blood A (air) . . contains, in 100 cc. . . O_2 16.9; CO_2 33.1

Blood B (oxygen, 1¾ atm.) contains, in 100 cc. O_2 21.4; CO_2 36.6

Blood C (oxygen, 7 atm.) . . contains, in 100 cc. O_2 32.5; CO_2 73.8; N 4.1

Blood D (air, 27 min. after decompression) contains, in 100 cc. O_2 16.9; CO_2 21.0

Blood E (air, 67 min. after decompression) . contains, in 100 cc. O_2 17.0; CO_2 31.5

The bag contained after the experiment a mixture of CO_2 10.7 and O_2 70 per cent.

Therefore the oxygen pressure when blood B was drawn was about 1.75 x 79 = 138, and when blood C was drawn, about 7 x 71 = 497.

Experiment CCLXXXII. December 3. Dog.

Tube in the trachea; rectal temperature 38°; respirations extraordinarily rapid.

3:20; blood drawn from the left carotid, 33 cc. . . . . A

The oxygen bag is attached to the cannula in the trachea; a flask at the bottom of which there are a few bits of potash is placed where the air will pass over it.

3:30; drew 33 cc. of blood considerably redder; respiration has become much slower. . . . . B

3:45; placed in the large compression apparatus.

4 o'clock; pressure is 3½ atmospheres; drew 33 cc. of very red blood; no gas. C

A series of petty accidents occur; at 4:40, I wish to decompress suddenly; but the rubber bag gets in front of the opening, and the decompression is not finished until 5:45.

The animal has neither convulsions nor quiverings; its temperature is 36°.

Blood A (air, normal pressure) . . contains . . . O_2 18.1; CO_2 24.9

Blood B (oxygen, normal pressure) contains . . . O_2 20.9; CO_2 33.7

Blood C (oxygen, 3½ atmospheres) contains . . . O_2 27.5; CO_2 56.5

The air of the bag contained before the experiment 85 per cent of oxygen; when blood C was drawn, the tension was about 80 x 3.5 = 280.

Experiment CCLXXXIII. December 10. Vigorous dog, weighing 12.5 kilos.

At 3:45, tube placed in the trachea; the respiration becomes panting.

3:55; drew 33 cc. of blood; the temperature is 38.5°. . . . . A

4:10; forced to breathe from the rubber bag containing oxygen.

4:18; drew 33 cc. of blood, redder. . . . . B

4:35; placed in the large apparatus with the rubber bag, in which a potash wash has been placed.

5:05; the pressure is 6 atmospheres; drew 38 cc. of blood. . . C

5:35; the pressure is 9 atmospheres; drew 35 cc. of blood. . . D

Some very small bubbles of gas appear.

5:38; decompression in 3 or 4 minutes.

When the animal is taken out, it is dead. The right auricle is still beating. The venous blood is quite red; and when it is caught in a glass, small bubbles of gas escape which come to the surface or remain clinging to the walls of the glass. Same phenomenon for the

arterial blood, only the bubbles are much smaller. The muscles and the motor nerves respond to electricity.

When I drew blood D, the blood came with great difficulty into the syringe in slow spurts. Probably the animal was dying at that very moment; he had been observed to breathe up to that time; afterwards, not.

At 7 o'clock, no rigor mortis.

Blood A (air, normal pressure) . . . . . O_2 19.8; CO_2 20.9; N 2.1
Blood B (oxygen at 88%, normal pressure) . O_2 20.9; CO_2 34.5; N 1.5
Blood C (oxygen, 6 atmospheres) . . . . . O_2 26.3; CO_2 63.5; N 3.9
Blood D (oxygen, 9 atmospheres) . . . . . O_2 30.7; CO_2 61.5; N 5.5

The air of the bag, before the experiment, contained 88 per cent of oxygen. So, taking account of the respiratory alteration, the oxygen tension, when blood C was drawn, could be expressed by 80 x 6 = 480, and when blood D was drawn, by 78 x 9 = 702.

Experiment CCLXXXIV. December 17. Young dog, weighing. 7.5 kilos.

3:30; rectal temperature 39°.

Tube placed in the trachea; respirations very rapid.

3:40; drew 33 cc. of blood from the carotid, not very red. . . . A

3:42; forced to breathe from the oxygen bag, with a potash wash in the bag.

3:50; rectal temperature, 38.8°; drew 33 cc. of very red blood. B

Placed in the compression apparatus at 4:05.

4:50; 7 atmospheres; we try in vain to extract blood.

Taken to 7 and ¾ atmospheres, and decompressed suddenly.

Withdrawn; temperature 37°. A few stiffenings and clonic convulsions. The heart beats slowly, the blood is very dark.

Dies at 5:10, without a last sigh, with complete resolution.

No urine in the bladder. But the kidneys, crushed with sulfate of soda and animal charcoal, give a yellow precipitate with very good Bareswill's reagent. The blood, treated in the same way, gives a similar enormous precipitate; the potash browns the boiling liquid.

Blood A (air, normal pressure) . . . . . contains O_2 12.1; CO_2 29.6
Blood B (oxygen at 91%, normal pressure) contains O_2 14.1; CO_2 24.5

The oxygen tension was about 7.75 x 80 = 620.

Experiment CCLXXXV. December 20. Very vigorous dog, weighing 16.5 kilos. Rectal temperature 38.5°.

3:55; drew 33 cc. of rather dark blood. Respirations a little slow. . . . . A

4 o'clock; tube in the trachea; very much exaggerated respirations for 4 to 5 minutes; then, period of calm, followed by other exaggerated respirations. At 4:10, while I am preparing to draw blood, the respirations grow calm and return to normal type. At 4:12, drew 33 cc. of blood, less dark. . . . . B

4:30; placed in the compression apparatus, with rubber bag.

5:05; pressure is 6 and ¾ atmospheres; drew 40 cc. of very red blood, from which very small bubbles of gas escape. C

5:12; decompressed suddenly.

When placed upon the table, has abundant froth in the mouth; is in very violent opisthotonos, replaced from time to time by a pleurosthotonos on the right side; at times strong clonic convulsions, with a few intervals of complete repose. During the attacks, respiration stops, and it is very difficult to detect the heart beats. The eye remains sensitive.

At 5:15, the temperature is 36.7°, and the pulse only 20.

At 5:30; respiratory rate 48, pulse 112.

At 5:38, a little while after a strong convulsion, I draw 33 cc. of very red blood. . . . . D

At 5:45, temperature 35°.

I had the dog inhale chloroform through the trachea; respiration is very active; the feet are then stiffened. Soon the respiration stops in its turn; the eyes are very much swollen.

I use artificial respiration; the heart resumes strongly enough, and respiration returns; then everything stops in spite of artificial respiration, and the animal dies about 6 o'clock.

The serum of the blood, treated by sulfate of soda and animal charcoal, gives with copper reagent a very abundant yellowish-red precipitate.

Blood A (air, normal pressure, normal respiration) O_2 15.1; CO_2 40.8
Blood B (air, normal pressure, tracheal respiration) O_2 20.3; CO_2 24.0
Blood C (oxygen, 6¾ atmospheres) . . . . . O_2 34.6; CO_2 92.5; N 3.6
Blood D (during convulsions) . . . . . O_2 19.0; CO_2 14.8

The composition of the air of the bag, before the experiment, being 80% of oxygen, the tension at the time of drawing blood was about 6.75 x 84 = 567.

Experiment CCLXXXVI. January 22. Temperature 16°. Large dog.

At 3:10, tube placed in the trachea; rectal temperature 39.5°.

At 3:30, the animal breathing slowly and deeply, 33 cc. of carotid blood drawn. . . . . A

At 3:40, dog is placed in the compression cylinder, with the rubber bag containing air with 88.6% oxygen.

At 4 o'clock, pressure is 4 atmospheres; then 33 cc. of very red blood drawn. . . . . B

At 4:15, pressure is 6½ atmospheres. Drew 38 cc. of very red blood, which coagulates very rapidly. C

At 4:17, decompressed in 2 minutes.

Taken out in strong convulsions. They consist of attacks of stiffness of the paws and of the body in opisthotonos, so strong *that the dog can be carried by one paw, like a piece of wood.* (See Fig. 61.) They can be brought on at will.

Rectal temperature 37°.

At 4:40, drew 33 cc. of moderately red blood; the temperature has dropped to 36°. . . . . D

The convulsions continue to decrease; the cannula is removed. At 5:35, the convulsions have stopped. I draw a little carotid blood, which, boiled with charcoal and sulfate of soda, gives a very strong

reduction of the copper reagent. Nothing by sulfate of lime or nitric acid.

The animal is placed in a cage fitted to collect the urine.

This urine, the next day, reduces copper reagent, *giving an abundant yellow precipitate.*

Blood A (air, normal pressure) . . . . O_2 15.8; CO_2 43.0
Blood B (oxygen; 4 atmospheres) . . . . . O_2 23.9; CO_2 59.0
Blood C (oxygen; 6½ atmospheres) . . . . . O_2 28.7; CO_2 69.4
Blood D (air; returned to normal pressure, convulsions) O_2 12.4; CO_2 9.9

The bag contained at the beginning air with 88.6% of oxygen.

At the moment when blood B was drawn, the oxygen tension was about equivalent to 320, representing 16 atmospheres. For blood C, the figures would be 480 and 24 atmospheres.

Experiment CCLXXXVII. January 23. Temperature 16°. Large dog.

Rectal temperature 39°. Tube placed in the trachea at 3:15. Its respiratory rhythm does not change noticeably; it was very rapid.

At 3:53, its temperature dropped to 38.5°. 33 cc. of moderately red blood drawn from the carotid. . . . . A

At 4:02, placed in the apparatus with the bag containing super-oxygenated air.

At 4:15, pressure is 2 and ¾ atmospheres.

I drew 45 cc. of very red blood, containing no free gases, with a manifest tendency to coagulation. An accident prevents me from analyzing it for its gaseous content.

At 4:38, pressure is 7¼ atmospheres.

I again draw 45 cc. of very red blood, coagulating rapidly, in which no free gases appeared. . . . . B

At 4:40, decompression in 2 minutes.

Taken out in strong convulsions. Rectal temperature 37°.

The convulsions, at first rather moderate, with intervals of flaccidity, continue to increase in strength. In the intervals of tonic convulsions, the animal moves its feet as if it were walking. The tonic convulsions are so strong that the animal can be lifted like a piece of wood, by one foot. Its feet are stiff, its body in right pleurosthotonos, with opisthotonos of the neck, its eyes open, protruding; the pupils dilated; it is vomiting.

At 5 o'clock it dies. The heart continues to beat for some minutes.

At 5:10, drew 33 cc. of very dark blood with a catheter from the left heart, which is no longer beating. C

There is no urine in the bladder; very severe pulmonary congestion.

Blood A (air, normal pressure) . . . . . O_2 17.2; CO_2 22.3
Blood B (oxygen, 7¼ atmospheres) . . . . . O_2 30.1; CO_2 72.3
Blood C (after death) . . . . . O_2 1.4; CO_2 29.0

The air of the rubber bag, analyzed after the animal had been taken from the apparatus, contained O_2 74%; CO_2 10%.

At the moment when blood B was drawn, the oxygen tension was about 540, equivalent to 27 atmospheres.

Experiment CCLXXXVIII. January 24, temperature 17°. Vigorous bulldog.

Rectal temperature 38.5°.

At 2:30, 33 cc. of carotid blood drawn; the animal breathes quietly, by natural channels. . . . . A

Tube placed in the trachea; respiration becomes much more rapid.

At 2:45, 33 cc. of blood drawn. . . . . B

At 3:25, the animal is placed in the apparatus, with the bag containing superoxygenated air.

At 3:45, pressure 4 atmospheres, 41 cc. of blood drawn. C

At 4:03, pressure has risen to 6 and ¾ atmospheres; 57 cc. of blood drawn. . . . . D

At 4:07, decompression in 3 minutes. Rectal temperature 37°; the animal is in strong convulsions.

At 4:33, the rectal temperature has fallen to 36°.

At 4:35, I administer chloroform; the first application causes convulsions, which soon cease, and the animal becomes insensible and in resolution. I stop administering chloroform at 4:45. Up to 5:55, there are no more convulsions. Then they reappear.

The animal survives.

Blood A (air, normal pressure, respiration by natural channels) O_2 16.0; CO_2 41.5

Blood B (air, normal pressure, tracheal respiration) O_2 23.4; CO_2 15.2

Blood C (oxygen, pressure 4 atmospheres) . . . O_2 28.5; CO_2 68.3

Blood D (oxygen, pressure 6¾ atmospheres) . . . O_2 30.7; CO_2 82.0

Since the bag from which the animal had breathed contained after the experiment 74.5% of oxygen and 8.6% of carbonic acid, we can reckon at 300 the oxygen tension at the moment when blood C was drawn, that is, 15 atmospheres of air, and at 510 at the moment when blood D was drawn, that is, 25 to 26 atmospheres.

Experiment CCLXXXIX. January 28. Large dog, fasting since the morning of January 27.

At 2:35, I draw 33 cc. of carotid blood, moderately red. . . . A

I mix a few cubic centimeters of it with distilled water, to examine it for sugar (*a*). The rectal temperature is 38°.

The trachea is not opened, but the muzzle, pictured in Figure 37, is fitted to the animal, and at 3:15 the dog is placed in the apparatus with the oxygen bag.

At 3:50, the pressure is 6¾ atmospheres. Decompression is made in 5 minutes.

The animal is in strong convulsions; tonic stiffenings, clonic convulsions. Attacks provoked at will.

At 4 o'clock, I draw during the convulsions 23 cc. of dark carotid blood. . . . . B

Rectal temperature is only 36.5°.

At 4:25, drew 33 cc. of moderately red blood; the animal has just had an attack. C

At 4:50, the temperature is only 36°.

At 5:10, another 33 cc. of blood, which is redder; the convulsions had ceased a few minutes before. . . . . D

At 6 o'clock, the animal is no longer in convulsions; when completely unfastened and placed on the floor, it walks like a hyena, hind quarters very low. It is set aside for the collection of the urine.

It does not urinate until the next day at 3 o'clock; no sugar. At that time, its temperature has risen to 39.5°.

Blood *a*, boiled with charcoal, does not reduce Fehling's solution.

On the contrary, a mixture of bloods B, C, D, boiled in a similar way, gives a very considerable reduction. A part of the colorless liquid obtained by boiling this blood with the addition of water and much charcoal, being placed on the drying-stove, with brewer's yeast, in a tube inverted over mercury, ferments and gives off a gas which is absorbed by potash. Another part, cooled with copper reagent, discolors it and precipitates.

Blood A (air, normal pressure) . . . . . contained O_2 16.0; CO_2 44.5
Blood B (in open air, convulsions) . . . . contained O_2 9.7; CO_2 48.2
Blood C (after 25 min. in the open air) contained O_2 13.9; CO_2 10.5
Blood D (after 1 h. 10 min. in the open air) contained O_2 18.5; CO_2 19.0

The air of the bag after the experiment contained 61.5% of oxygen and 12.9% of carbonic acid. The oxygen tension had risen to nearly 420, that is, 21 atmospheres of air.

Experiment CCXC. February 4. Large dog, which had not eaten since the day before in the morning. Rectal temperature 37.5°.

At 3:15, 33 cc. of rather red blood drawn from the carotid. . . A

A small quantity of this blood is boiled with water, sulfate of soda, and charcoal.

The animal, furnished with the muzzle and the oxygen bag, is placed in the apparatus at 4 o'clock.

At 4:40, I make the decompression in a few minutes; the pressure had reached 7½ atmospheres.

The animal is in excitable convulsions; its temperature is only 36°.

At 5:20, drew 33 cc. of very red blood. . . . . B

The animal had just had convulsions, and in the interval breathed very rapidly.

At 5:40, drew another 33 cc. of blood. C

The convulsions are over at the time; the animal, when unfastened, cannot walk.

It survives; the urine which it voids during the night contains no sugar; the very abundant saliva found in the muzzle did not contain any either. On the other hand, blood B was certainly richer in sugar than blood A.

Blood A (before the experiment) . . . . . contained O_2 18.7; CO_2 44.0
Blood B (afterwards, during the convuls.) contained O_2 23.2; CO_2 19.4
Blood C (convulsions over) . . . . . contained O_2 20.3; CO_2 22.0

The air of the bag, after the experiment, contained 57.6% of oxygen and 7.4% of carbonic acid.

The oxygen tension had therefore risen to about 440, that is, 22 atmospheres.

Experiment CCXCI. February 5. Terrier, medium size, fasting since the preceding evening.

Rectal temperature 39.5°.

At 5 o'clock, put into the apparatus with the muzzle and the oxygen bag.

At 5:40, pressure is 7 and ⅓ atmospheres.

From 5:40 to 5:45, decompression.

Is in strong convulsions, with violent snapping of the teeth. Temperature 38°.

Dies at 6 o'clock.

The air of the bag, after the experiment, contained 77.2% of oxygen and 8% of carbonic acid.

The oxygen tension had been about 560, corresponding to 28 atmospheres of air.

Experiment CCXCII. February 7. Vigorous poodle.

Temperature 39.8°.

Took blood from the carotid to analyze for sugar. . . . . *a*

At 4 o'clock, muzzle and oxygen bag; the compression begins.

At 4:43, the pressure is 7¼ atmospheres; rapid decompression. Taken out of the apparatus, the dog has 2 or 3 convulsions; its temperature is 38°; it dies while we are drawing a little very dark arterial blood, which is treated with sulfate of soda. . . . . *b*

a and *b* are treated in the same way, with the same addition of water and according to the method of Cl. Bernard. Now 5 cc. of the filtered liquid furnished by *a* reduce only 10 drops of copper reagent, while the same volume of the liquid in *b* reduces 15.

The air of the bag before the experiment contained 90% of oxygen. After the experiment, there was only 76.5% with 10.7% of carbonic acid.

The oxygen tension had therefore risen to about 600, which corresponds to 30 atmospheres of air.

Experiment CCXCIII. February 18. Dog weighing 10 kilos, fasting since the morning of February 17. Rectal temperature 40°.

At 1:30, I put a tube in its trachea.

At 2 o'clock, its rectal temperature is only 39.8°.

From 2:05 to 2:20 (15 minutes), I force it to inspire and expire in a rubber bag containing 41 liters of air; towards the end, the animal experiences a certain respiratory difficulty, takes great inspirations, and struggles a little. I call the air of this bag *a*.

At 2:45, I take 25 gm. of blood from the carotid and mix it with 25 gm. of sulfate of soda and 10 gm. of distilled water . . . . *x*

At 2:55, put into the compression apparatus, with the oxygen bag, in which is a little alkalinized water.

At 3:16, pressure is 5½ atmospheres; decompression in 2½ minutes. The dog displays only slight convulsions, lasting hardly quarter of an hour. He has salivated very abundantly; his temperature is 38°.

At 3:25, drew 25 gm. of carotid blood which is treated like blood *x* . . . . . *y*

At 3:40, drew 33 cc. of blood; the animal has been breathing quietly for some time. . . . . A

From 3:43 to 3:58 (15 minutes), I make the dog breathe in a bag containing the same quantity of air as bag *a*; I call this air b. The animal suffers also at the end of this respiratory period.

At 4:20, the animal being very quiet, I draw 33 cc. of carotid blood. . . . . B

At 4:45, rectal temperature 36.5°.

At 6 o'clock, drew 33 cc. of blood. C

Immediately after, his temperature is 37°.

At 6:15, I draw more blood which I treat like *x* and *y* . . . . . *z*

Rectal temperature 37°.

I remove the tracheal cannula; the dog can walk a little. At 7:10, his temperature has risen to 39°. He survives.

Since the air of the bag contained before the experiment 90.8% of oxygen, and after the experiment, 77.3% of oxygen and 8.4% of carbonic acid, the tension rose to 440, that is, 22 atmospheres of air.

Blood A (22 min. after the decompression) contained O_2 17.5; CO_2 20.0

Blood B (1 hour after the decompression) contained O_2 17.2; CO_2 17.0

Blood C (2 hours 40 minutes after the decompression) contained O_2 16.3; CO_2 26.5

The liquids produced by boiling bloods *x*, *y* and *z* give the following results:

5 cc. of the liquid furnished by *x* (before the compression) discolor 15 drops of copper reagent.

5 cc. of the liquid furnished by *y* (10 minutes after the decompression) discolor 35 drops of copper reagent.

5 cc. of liquid furnished by *z* (3 hours after the decompression) discolor 15 drops of copper reagent.

The analyses of airs *a* and b show that:

1. In *a*, before oxygenated compression, the dog consumed in 15 minutes 4.89 liters of oxygen, and produced 2.99 liters of CO_2; that is, in one hour 15.56 liters of oxygen and 9.98 liters of CO_2.

2. In b, after the compression, the dog consumed in 25 minutes only 3.37 liters of oxygen, and produced only 1.88 liters of CO_2; that is, in one hour 8.88 liters of oxygen and 4.51 liters of CO_2.

Experiment CCXCIV. February 23. Strong female spaniel.

Rectal temperature 39°.

At 2:15, I put a tube into the trachea: the respirations become very rapid, 110; pulse 120.

At 2:40, took from the carotid 25 gm. of blood, which is treated as usual in the test for sugar. . . . . *x*

At 2:40, the rectal temperature is 38°. The respiration grows calm, and falls to 40 per minute.

From 2:45 to 3 o'clock (15 minutes), the animal breathes in a closed bag, containing 47.14 liters of air. The breathing, calm at first, becomes difficult at the end of 7 or 8 minutes. I call the air of this bag. . . . . *a*

At 2:45, the rectal temperature is still 38°.

At 3:15, put into the apparatus with the oxygen bag.

At 3:40, pressure is 6 and ¾ atmospheres; decompressed sud-

denly. Is in quite strong convulsions. White foam very abundant in the mouth.

Rectal temperature 37°.

At 3:45, drew a little blood for sugar analysis; the animal is in convulsions. . . . . *y*

At 4 o'clock, the animal is calm; respiratory rate 14, pulse 60.

From 4:12 to 4:27 (15 minutes), made to breathe in the same quantity of pure air as above. . . . . b

The respirations remain calm the whole time.

At 5 o'clock, rectal temperature still 37°. The animal, when put on the floor, walks quite well. It survives.

The air of the oxygen bag contained at the beginning of the experiment 86.4% of oxygen; at the end, it contained only 68.1% with 10.4% of carbonic acid. The oxygen tension then must have risen to about 460, or 23 atmospheres.

The liquid furnished by blood *x* discolors per 5 cc. between 10 and 15 drops of copper reagent; that of blood *y* discolors between 15 and 20.

As to the consumption of oxygen, it was in experiment *a* 3.95 liters, and in experiment b it fell to 2.15 liters. The production of carbonic acid also dropped from 2.41 liters to 1.99 liters.

Experiment CCXCV. February 24. Female dog weighing 17 kilos.

2:55; respiration by natural channels, calm; vaginal temperature 40°. I draw 33 cc. of carotid blood. . . . . A

3:12; I place a tube in the trachea; rapid respirations; then I take 500 gm. of arterial blood.

3:47; took 25 cc. of blood (temperature 39°). . . . . B

From 4:10 to 4:40, placed in the apparatus with a bag containing air with 93% oxygen. Pressure rises to 6 and ¾ atmospheres.

Decompressed suddenly, found dead, limp, temperature 37°.

The oxygen tension had risen to about 580, that is, 29 atmospheres of air.

Blood A (natural respiration) . . . . . O_2 17.0; CO_2 38.5
Blood B (tracheal respiration, copious bleeding) O_2 16.5; CO_2 14.4

Experiment CCXCVI. February 25. Dog weighing 15 kilos.

While he is breathing by the natural channels, I draw 33 cc. of carotid blood. . . . . A

Rectal temperature is 40°.

I then place a tube in the trachea, and extract in one hour 400 cc. of arterial blood. He does not make any extraordinary or rapid respirations, but his temperature drops to 37.5°; I take the last 33 cc. of blood for analysis. . . . . B

From 3:45 to 4:40, raised to the pressure of 6½ atmospheres, with a bag containing air with 90% of oxygen.

Taken out in strong convulsions, excitable by the introduction of the thermometer into the rectum. Temperature 36°.

The convulsions continue, and the animal dies during the night.

The maximum oxygen tension was about 520, corresponding to 26 atmospheres of air.

Blood A (natural respiration) . . . . . O_2 19.0; CO_2 42.0
Blood B (tracheal respiration, copious bleeding) . . O_2 13.1; CO_2 13.2

Experiment CCXCVII. May 24, 1874. Experiment made before the committee of the Academy of Sciences.

Female dog of moderate size. Tube in the trachea. Oxygen bag.

Compression taken to 7 atmospheres. At that time (5:30), I draw 35 cc. of carotid blood, from which some free gases escape. This blood contains 33.2 cc. of oxygen per 100 cc. of blood, 76 of carbonic acid, and 6.6 of nitrogen.

Sudden decompression at 5:35; the animal has no convulsions. A quarter of an hour afterwards, they occur in fits, and can be produced; at certain moments, the dog becomes as stiff as wood.

She is chloroformed; the convulsions cease, but reappear when consciousness returns. At 6:30, lying on her side, constantly makes the movements of walking with her two front feet.

At 7:30, rigidity again.

The next day, at noon, this rigidity persists. The animal has remained all night lying on the ground, without having moved from the spot. The eye lacks sensitivity, the pupil does not react to light; the rectal temperature is 23°, that of the room being 19°.

The dog dies during the day.

I hope that the reader will not object to this long series of descriptions. The symptoms which I am studying at present seemed to me so important that it was necessary to give many examples in detail. The questions which present themselves are numerous. We are now well enough informed to settle almost all of them.

But first, according to our custom, we should draw up a table (Table XV) which summarizes the principal results of the data which we have just reported. I listed the experiments according to the increasing oxygen tension, expressed in Column 4 by its real value, and in Column 5 by the equivalent in atmospheres.

We are now ready to make a complete description of the fatal effects of oxygen, to describe its symptoms, and even to analyze the mechanism of the poisoning.

Let us first discuss the concentrations.

The convulsive symptoms, as Columns 5 and 10 of the table show us, did not appear clearly until about 19 atmospheres. Dogs, then, seem a little less sensitive than birds, upon comparing this result with that in Table XIV. That would not be surprising, but I do not hesitate to say that on this point my experiments do not furnish sufficiently definite information.

I can only say that the duration of the compression has much to do with the intensity of the symptoms of oxygen poisoning.

Table XV

Experiment number	Duration of the compression	Barometric Pressure in atmospheres	Tension of O_2 in the bag $O_2 \times P$	Value of tension in atm. Round numbers $O_2 \times P$ / 20.9	Tension of CO_2 in the bag $CO_2 \times P$	Composition of gases of the blood O_2	Composition of gases of the blood CO_2	Rectal Temperature (degrees)	Symptoms and Observations
	min.								
CCLXXXII	—	Air; trachea; resp. very rapid	---	---	------	18.1	24.9	38.0	Decompression in 1 hour. No convulsions noted.
		Oxyg.: resp. slow	280	4.2	------	20.9	33.7		
		3½ atm.		14	Potash	27.5	56.5	36.0	
CCLXXIX	30	Free air; trachea	---	---	------	17.0	39.0	39.4	Mild convulsions; *survived.*
		5	380	19	40.5	24.8	75.0	36.5	
CCLXXXIX	35	Air, natural resp.	---	---	------	16.0	44.5	38.0	Strong convulsions. Much sugar in the blood; *survived.*
		6¾	420	21	86.2	---	---	----	
		Air; 5 min. after compression	---	---	------	9.7	48.2	36.5	
		Air; 30 min. id.	---	---	------	13.9	10.5		
		Air; 1 hr. 15 min. id.	---	---	------	18.5	19.0	36.0	
CCXC	40	Air; natural resp.	---	---	---	18.7	44.0	37.5	Strong convulsions. Sugar in the blood; *survived.*
		7½	440	22	55.5	---	---	36.0	
		Air; 30 min. after	---	---	------	23.2	19.4	----	
		Air; 50 min. after	---	---	------	20.3	22.0	----	
CCXCIII	—	Air; trachea	---	---	------	---	---	40.0	Weak convulsions; *survived.* O_2 consumption less after than before. Much sugar in the blood.
		5½	420	22	Potash	---	---	38.0	
		Air; 22 min. after decompress.	---	---	------	17.5	20.0	---	
		Id. 1 hr. id.	---	---	------	17.2	17.0	37.0	
		Id. 2 hr. 40 min. id.	---	---	------	16.3	26.5	37.0	
CCXCIV	25	Air; resp. tracheal	---	---	------	---	---	38.0	Moderate convulsions; *survived.* O_2 consumption less after than before. Sugar in blood.
		6¾	460	23	70.2	---	---	37.0	

CCLXXXVI	40	Air; trachea	---	---	------	15.8	43.0	39.5	Strong convulsions;
		4	320	16	------	23.9	59.0	----	*survived.*
		6½	480	24	------	28.7	69.4	37.0	Sugar in blood and urine.
		Air; after 20 min.	---	---	------	12.4	9.9	36.0	
CCLXXXI	45	Air; trachea	--	--	------	14.9	31.1	38.5	Severe convulsions;
		1¾	140	7	------	21.4	34.3	--	quieted with chloroform;
		7	500	25	74.9	32.5	73.8	38.5	*survived.*
		Free air; 27 min. after	---	---	------	16.9	21.0	39.0	
		67 min. after	---	---	------	17.0	31.5	----	
CCLXXXVIII	45	Air; natural resp.	---	--	------	16.0	41.5	38.5	Strong convulsions;
		Id. tracheal resp.	---	---	------	23.4	15.2	----	chloroform; *survived.*
		4	300	15	------	28.5	68.3	----	
		6¾	510	25.5	58.0	30.7	82.0	37.0	
CCXCVI	55	——	520	26	------	---	---	----	Convulsions; *died* during night.
CCLXXVIII	50	Free air; tracheal tube	--	---	------	15.5	22.9	36.0	Violent convulsions; *died*
		5	350	17.5	------	24.0	63.0	----	next day, still in con-
		7	480	24.0	------	31.5	54.6	----	vulsions.
		8	530	26.5	43.2	---	---	30.0	
CCXCVII	—	Tracheal resp.	---	---	------	--	--	----	Strong convulsions;
		7	---	---	------	33.2	76.0	----	chloroform; *died* next day.
CCLXXXVII	40	Air; trachea	--	--	------	17.2	22.3	38.5	Strong convulsions; *died*
		7¼	540	27	72.5	30.1	72.3	37.0	in 20 minutes.
		After death	---	---	------	1.4	29.0	----	
CCLXXX	50	Free air; trachea	--	--	------	14.4	41.0	38.1	Convulsions; *died* in 1 hr.;
		7	520	26.0	------	24.1	68.5	--	sugar in urine.
		7¼	550	27.5	Potash			36.0	
		Free air; 40 min. after	--	--	------	15.8	16.5		
		Id. 70 min. after	---	---	------	15.8	28.3	34.0	

Table XV—Concluded

Experiment number	Duration of the compression	Barometric Pressure in atmospheres	Tension of O_2 in the bag $O_2 \times P$	Value of tension in atm. Round numbers $\frac{O_2 \times P}{20.9}$	Tenison of Co_2 in the bag $CO_2 \times P$	Composition of gases of the blood O_2	Composition of gases of the blood CO_2	Rectal Temperature (degrees)	Symptoms and Observations
	min.								
CCLXXXV	42	Air; resp. normal	---	---	------	15.1	40.8	38.5	Convulsions violent; *died* in 45 min.; much sugar in blood.
		Id. trachea	---	---	------	20.3	24.0	----	
		6¾	560	28	------	34.6	92.5	36.7	
		Air; after 25 min.	---	---	------	19.0	14.8	35.0	
CCXCI	45	Air; natural resp.	---	---	------	---	---	39.5	Strong convulsions; *died* in 15 minutes.
		7⅓	560	28	58.4	---	---	38.0	
CCXCV	30	——	580	29	------	---	---	----	*Died* in the apparatus.
CCXCII	45	Air; natural resp.	---	---	------	---	---	39.8	*Died* in a few minutes.
		7¼	600	30	77.6	---	---	38.0	Sugar in the blood.
CCLXXXIV	55	Air; trachea	-	-	------	12.1	29.6	39.0	*Died* in 10 minutes.
		Oxygen	90	4.5	------	14.1	24.5	38.8	
		7¾	620	31	Potash	---	---	37.0	
CCLXXXIII	65	Air; trachea; resp. very rapid	-	---	------	19.8	20.9	38.5	Dead when removed from the apparatus.
		Oxygen	88	4.4	------	20.9	34.5	----	
		6	480	24	------	26.3	63.5	----	
		9	700	35	Potash	30.7	61.5	----	

I have sometimes seen them occur at pressures hardly over 10 atmospheres of air, and even result in death. Here, for example, are three experiments.

Experiment CCXCVIII. April 26. A rabbit and two sparrows are placed in the large compressed air receiver.

From 1:45 to 2:45, the pressure is raised to 10 atmospheres.

About 5 o'clock, on looking through the windows of the apparatus, we see the animals are dead.

Experiment CCXCIX. April 30. Dog weighing 4.300 kilos. At 9:45, placed, free, in the large receiver.

The pressure is raised to 10 atmospheres at 10;30; then the little exhaust cock is opened, so that a current of air under 10 atmospheres is maintained; the pressure even rises to 11 atmospheres at 10:45; at that time we look in through the portholes and see the dog lying on its back, in a kind of convulsion. The pressure is lowered to 10, and almost immediately the animal recovers, stands up on his feet, and barks wildly.

At noon, the pressure is still 10 atmospheres; the dog has remained standing and begins to bark furiously when anyone approaches the apparatus.

The current of air under pressure is maintained.

At 2:15, the animal is lying down, struggling half convulsively.

It dies at 5 o'clock; as the cock has been closed for some time, a sample of air is taken which appears practically pure (O_2 19.8; CO_2 0.4).

Experiment CCC. February 15. Two mountain sparrows are kept, from 11:30 to 5:30, under a pressure of air varying from 8½ to 9½ atmospheres; constant current of air.

One of them (A), at the end of a stay of several hours, gives increasing signs of discomfort.

Very slow decompression. A is much weakened, has convulsive movements of the wings, feet, and tail; its temperature, which was 41° at the beginning, is only 33.8°. At 7 o'clock in the evening, it still has convulsive movements, leans backward on its tail.

The other sparrow seems quite well. Its temperature is 39°.

Both die during the night.

I do not dwell on these last experiments. To return to those summarized in Table XV, we see that though for compressions of short duration convulsions begin to appear with an oxygen tension a little lower than the value of 19 atmospheres of air, they are strong and constant above 20 atmospheres, and always entail a very rapid death when above 27 atmospheres. In the only experiment (Experiment CCLXXXIII) in which the oxygen tension rose to the value of 35 atmospheres, the animal was already dead when taken from the apparatus.

Let us consider now the oxygen content of the arterial blood,

as shown in Column 7 of the table. We find rather large differences there. Whereas, for example, in Experiment CCLXXXI, in which the oxygen proportion rose from 14.9 to 32.5, although seized by violent convulsions, the animal survived, the dog in Experiment CCLXXXVII died in 20 minutes, without having in its blood more than 30.1% of oxygen, the initial proportion being 17.2. All the results show that it would be impossible to fix exactly either the absolute quantity of oxygen with which convulsions and death occur or its proportional increase. Yet whenever the animal died, the quantity of oxygen always exceeded 30 volumes per 100 volumes of blood.

The average increase is, we see, very slight, since it oscillates between a third or a half above what exists normally.

If, in order to examine their general course with more profit, we express by graphs, in our usual manner, the results contained in Column 7, we get Figure 60. The many variations which we noted are shown here very clearly.

But if we slide all these lines up vertically, making the origin of each the number 20, and if we take the average of the different points corresponding to about the same pressure, we get definitely a line — — — of remarkable regularity, that is, a straight line.

So, in the living animal, we find confirmed the experiments *in vitro* included in Subchapter V of Chapter II: from one atmosphere on, there is added to the blood only dissolved oxygen.

It is a fact worth noting that convulsions may appear when the blood has an oxygen content appearing sometimes in healthy animals, which they may almost reach after rapid respiration. We see first then that it is not the proportion of oxygen contained in the blood which is of itself dangerous; we see next that the increase of this proportion, even to a high degree, does not constitute the danger. This increase must be permanent, must be the result, not of a better saturation of the corpuscles as an effect of more complete aeration, a saturation which the reducing action of the tissues soon restores to the normal degree, but of a saturation due to the fact that the tissues themselves are saturated with oxygen and in equilibrium with the blood.

That is why the convulsions occur only after the compression has lasted some time. The tissues must be impregnated with oxygen in addition to what the blood, loaded with it in the lungs, brings them and incessantly gives over to them.

At the beginning of these experiments I asked myself whether the blood was not directly altered by the excess of oxygen, and did

not thus become the cause of the convulsive symptoms. Inspection of the corpuscles through the microscope, it is true, showed me no alteration of forms and dimensions; but that did not satisfy me. I

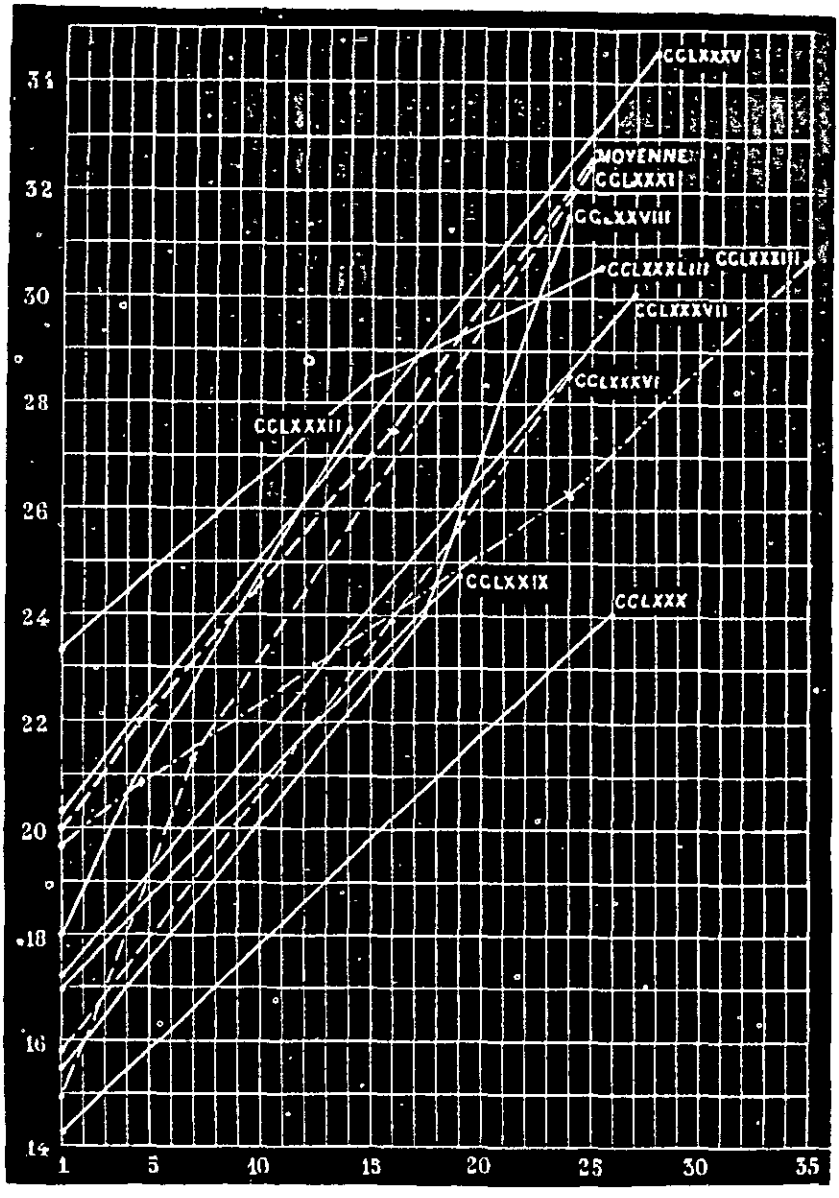

Fig. 60—Dogs poisoned by oxygen: increasing oxygen content of their arterial blood.

resolved then to inject into a healthy dog blood which had been greatly superoxygenated. I did so in the following experiments.

Experiment CCCI. June 30. Defibrinated dog blood, shaken in the apparatus pictured in Figure 45, under a pressure of 10 atmospheres of air with 65% of oxygen. Next the excess of gas was expelled by whirling the flask containing the blood at the end of a cord, like a sling. It then contained 24 volumes of oxygen per 100 volumes of blood. I injected 200 cc. of it into the femoral vein of a female dog weighing 6 kilos.

No symptom, not even apparent discomfort.

Experiment CCCII. July 23. Defibrinated dog blood; treated like the preceding at 10 superoxygenated atmospheres; it contained 34 volumes of oxygen.

I bled a little dog weighing 1640 gm. from the carotid; I took from him 20 cc. of very red blood (this blood clotted with extraordinary rapidity), containing only 7.3% of oxygen, with 33% of carbonic acid; the arterial pressure was 13 cm.

I injected into his jugular vein 35 cc. of the blood supersaturated with oxygen, which had been whirled like a sling.

No effect.

Experiment CCCIII. August 10. Defibrinated dog blood, treated as above, at 10 superoxygenated atmospheres; contained 33 volumes of oxygen.

Little dog weighing 2085 gm.; rectal temperature 36°; pulse 160; respiratory rate 50. I took 100 cc. of blood from him; he became very weak; his temperature fell to 34.5°; pulse 128; respiratory rate 30.

I then injected into his jugular 110 cc. of superoxygenated blood; immediately the animal revives, and when put down on the floor, seems only a little weak.

No after-effect.

And so in conditions of compression, that is, oxygen saturation, similar to and even greater than those which caused death, the blood acquired no dangerous quality, and can be substituted safely, in a very great proportion (1/19 of the weight of the body) for the blood of another animal. I must add that the agitation in compressed oxygen had lasted only a very short time, less than one hour. We shall see in Subchapter III of Chapter VI other experiments made from another point of view with blood shaken for several hours with compressed oxygen.

But let us come to the description of the convulsive attack itself. It is truly curious and terrifying.

Let us take a case of average intensity. When the animal is taken from the apparatus, it is generally in severe tonic convulsions; the four feet are stiff, the trunk is bent back or a little to

one side, the eyes protrude, the pupils are dilated, the jaws are clenched. Ophthalmoscopic examination shows copious hemorrhage at the back of the eye. Soon there occurs a sort of relaxing to which succeeds a new fit of stiffness with clonic convulsions resembling both a strychnine crisis and an attack of tetanus. These fits during the intervals of which the dog does not relax completely, but remains in opisthotonos, breathing with great difficulty, check the respiration, the heart still continuing to beat, although often with surprising slowness; the arterial pressure drops considerably. Sensitivity remains and one can excite new convulsions by it. After some time, these convulsive periods, which at first appear every five or six minutes, become rarer, then less violent; the stiffness

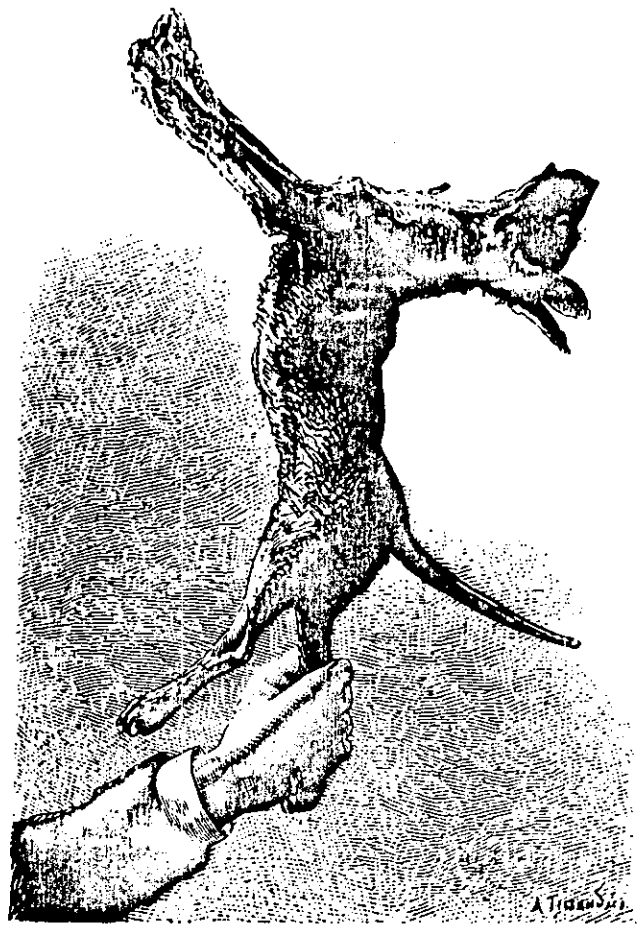

Fig. 61—Dog during the tonic convulsions of oxygen poisoning.

lessens in the intervals, and finally all symptoms disappear at the end of a few minutes or, at the most, a few hours.

In lighter cases, instead of attacks so violent that one can *lift the animal by a single foot, stiff as a piece of wood*, as Figure 61 shows, we observe irregular movements, local convulsions, symptoms, in a word, which are much like those of poisoning by phenol. We sometimes see acts which seem to indicate a certain mental disturbance.

In very serious cases, on the contrary, the stiffness is continual, with a few clonic increases from time to time; the teeth grind and clench so as to appear nearly ready to break, and death may occur after one or two attacks, separated by a few minutes. We then find the blood red, even in the portal system; then it turns dark. When the animal no longer makes any movement, the heart still continues to beat for a few minutes. At other times, as in Experiments CCLXXVIII and CCXCVII, the convulsions last nearly 24 hours before ending in death.

We find no congestions or ecchymoses in the lungs and the nervous centers. Only consistently in sparrows, we see the cranial diploe filled with a hemorrhage in dots, in smaller or larger spots, or even in a sheet covering the occipital region, and, in the most violent cases, the whole extent of the cranium. These bloody suffusions, the cause of which does not seem to me easy to explain, are invariably present in oxygen poisoning. They appear some time before the moment of death. But they are not peculiar to this kind of death, and in the preceding experiments we find them noted, even in simple asphyxia, under diminution of pressure (See Experiments CCLII and CCLIII).

The appearance of the symptoms which we have just described seems to indicate that the toxic action produces its effect on the nervous centers, as do strychnine, phenol, and other poisons which cause convulsions. This conjecture is corroborated by the fact that inhalations of chloroform stop the convulsions momentarily, although they reappear when the anesthesia has worn off. Let us remember that, according to our experiments on frogs, if the sciatic nerve has been cut in the hind leg, there are no convulsions in the muscles animated by this nerve.

To summarize all these facts, I shall quote here the conclusions of the report which I had the honor to make on this subject to the Academy of Sciences, February 17, 1873.

1. Oxygen acts like a poison which is rapidly fatal, when its quantity in the arterial blood rises to about 35 cubic centimeters per 100 cubic centimeters of liquid;

2. The poisoning is characterized by convulsions which, according to the intensity of the symptoms, represent the different types of tetanus, strychnine, phenol, epilepsy, etc.;

3. These symptoms, which are quieted by chloroform, are due to an exaggeration of the excito-motor power of the spinal cord;

4. They are accompanied by a considerable and constant drop of the body temperature.

It is this last point, purposely set aside until now, that I shall discuss next.

2. *The Diminution of Oxidations by Oxygen Poisoning.*

When for the first time I saw a sparrow struggling in violent convulsions under the influence of compressed oxygen, I imagined at first that the intra-organic oxidations had been so overstimulated in this bird that it was dying from burning itself out too quickly, producing thus a quantity of exaggerated heat, which perhaps became the direct cause of death. I thought therefore that the thermometer would show me a rise in the bird's temperature. Great was my surprise when I noted an absolutely opposite result.

In fact, in all the experiments, as the numbers listed in Column 5 of Table XIV and Column 9 of Table XV show, the temperature of the experimental animals dropped considerably, before and during the convulsions due to the oxygen.

At the beginning of the poisoning, when the convulsive symptoms were just commencing to appear, the temperature fell (Experiments CCLXI, CCLXII, CCLXVII). During the convulsions, it falls more, and when the convulsions are to end in death, it reaches very low figures (Experiments CCXCIII, CCLXXXI, CCLXXVIII, CCXCVII), especially in birds, in which it goes below 30, and sometimes even below 20 degrees (Experiment CXXXVII).

If, on the contrary, the animal is to survive, its temperature rises and returns in a few hours to its normal value (Experiments CCLX, CCLXII, CCLXVII, CCLXXXIX, CCXCIII).

It is, therefore, a firmly established fact that the excess of oxygenation of the organism results in a diminution of intensity in the chemical acts which produce the animal heat.

If the falling of the temperature of the body has given us a certain though indirect demonstration of this strange fact, we should find the direct proof when we examine either the absorp-

tion of the oxygen or the two important excretions of urea and carbonic acid.

Pulmonary exchange. Let us speak first of the consumption of oxygen and the production of carbonic acid, which are measured by the same experiment.

The experiments reported in Chapter I on birds which died in confined and compressed air show that these two phenomena lessened in intensity during the compression. But it is not possible to draw any conclusion, because the carbonic acid which is stored up in the tissues of the animal adds its action to that of the oxygen, and we shall see in Chapter VIII that carbonic acid also diminishes the oxidations.

As to the experiments reported in the present chapter, they cannot furnish any information as to what takes place during the compression.

I therefore had to plan special experiments; unfortunately, the problem presented more serious difficulties than one might have supposed at first glance.

In dealing with animals kept in closed vessels, as the idea was to turn out, for the reason which has just been stated it was necessary to eliminate the carbonic acid and keep to the measurement of the oxygen consumed. Now under the influence of pressure, there must be dissolved, in the very body of the animal, a certain quantity of oxygen which it is impossible to estimate and subtract from the total quantity of oxygen that has disappeared.

That is not all. In the numerous experiments which I have tried by this method, I took care always to act comparatively, to put simultaneously two identical animals, one under a bell of known capacity at normal pressure, the other in a compression receiver at a determined pressure, with a potash solution which absorbed the carbonic acid as it was formed. After a certain time had elapsed, I analyzed the two airs, and I could easily determine the quantity of oxygen absorbed by each of the two animals during a certain unit of time. Unfortunately, the percentage analyses made necessarily upon a small volume taken from the total mass of air in the experiment have to be multiplied by this mass, to get the total consumption, and the causes of error of either chemical or physiological nature then assume a value so great that they exceeded the differences noted between the two analyses.

I therefore had to give up this type of experiment completely. I used two others, which are not subject to the same criticism.

The first is a little indirect. It consists of comparing the quantity

of carbonic acid given off by the same animal placed successively in a closed vessel, in ordinary air or in a superoxygenated air at the same degree of compression. The special action of the carbonic acid is thus eliminated, because it is obviously the same in both cases. Here are the details of an experiment conducted in this way.

Experiment CCCIV. Albino rat. Rectal temperature 38°. May 10. Placed from 4:05 to 6:35 (2 hours 30 minutes) in the large receiver made of a mercury bottle (containing 3 liters), under a pressure of 3¼ atmospheres of air. When he is taken out, his temperature has fallen to 30°; he is quite sick, breathes slowly and deeply, but recovers quite quickly.

The air of the flask contains 12.5% of oxygen, and 6.6% of carbonic acid.

May 12. The animal has recovered perfectly; we begin again the same experiment, as to pressure and length; but this time we use air containing about 60% of oxygen. The tension of this gas corresponds then to that of compressed air from 9 to 10 atmospheres.

At decompression, the animal is found very low, not sensitive to pinching, but sensitive in the cornea. His rectal temperature is only 23.8°. He does not move, and dies at the end of a half-hour; no gas in the blood vessels.

The air in the receiver contained only 5.3% of carbonic acid.

Experiment CCCV. July 1. A. Two sparrows weighing together 38 gm. are subjected to a pressure of 5 atmospheres of air for 32 minutes, in the Seltzer water receiver.

Taken out after sudden decompression, seem very well, with slight bloody suffusions on the cranium.

During this time they consumed 3.9% of oxygen, and produced 2.8% of carbonic acid.

B. Two other sparrows, weighing together 39 gm., are placed next in the same apparatus, at the same pressure, but in air containing 72.6% of oxygen; the tension, 5 x 72.6 = 363.0, corresponds to about that of 18 atmospheres of air. They remain in the apparatus for 27 minutes.

At the end of 5 minutes there occurred in the two birds convulsions which lasted with intensity for 15 minutes. Then the sparrows remain lying on their backs, panting heavily.

One of them dies at the end of an hour; the other, after seeming to recover, but keeping up incessant muscular quiverings, is seized with convulsions after an hour and a half, and dies in a half hour.

Both immediately take on rigor mortis; moderate bloody suffusions.

In 27 minutes they consumed 2.05% of oxygen, 1.07 in the first 17 minutes and only 0.35 in the last 10; they produced in the first 17 minutes 1.07% of carbonic acid, and 0.28 in the rest of the time, in all 1.35.

We see from these figures that in 10 minutes at 3 atmospheres of air 1.2% of oxygen was consumed and 0.8% of carbonic acid was

formed, while at a tension corresponding to 18 atmospheres of air the consumption was only 0.7 and the production 0.5.

These experiments show very clearly that the absorption of oxygen and the production of carbonic acid decrease when the oxygen tension increases; the difference increases in proportion to the length of the experiment. Experiment CCCVI shows that at 9 or 10 atmospheres of air this effect is produced clearly, and that at this low pressure death may occur after an exposure that has been prolonged enough.

The second experimental method I used consisted of collecting and measuring all the carbonic acid produced by an animal during a certain time under different pressures but in a current of air that is always pure.

Experiment CCCVI. Rat weighing 160 gm.

July 28. Placed for a half hour in the Seltzer water apparatus, at normal pressure, under a current of air providing 2 liters per minute. The apparatus is immersed in water at 20°. The air which escapes is collected in a bag, and then connected with the potash bubbler of Figure 65, which absorbs all the carbonic acid from it; the carbonic acid is then extracted by one stroke in the mercury pump.

The temperature of the animal dropped from 38° to 37.5°.

It produced 247 cc. of carbonic acid.

August 2. Same animal, same general arrangements.

Kept under a current of air but this time at a pressure of 9 atmospheres, during the same length of time.

On being taken from the apparatus, its temperature has dropped from 38.1° to 34.6°.

Produced 176 cc. of carbonic acid.

In two of the experiments (CCXCIII and CCXCIV) made on dogs, which were reported in the preceding subchapter, I measured the oxygen consumption, and at the same time the production of carbonic acid, not during the compression, but during the moments following the decompression, and even in the midst of an attack of convulsions.

This measurement was interesting only from the comparative point of view. The method which I used, which makes no claim to absolute accuracy, allows me to compare what a dog was capable of absorbing and producing before being subjected to compressed air with what he consumes and produces when he has been taken from the cylinder.

The experimental animals had a tube in the trachea. I connected this tube with a bag filled with a known volume of air and let the animal breathe into the bag for a certain time. Since the

operation was repeated several minutes after the decompression, two chemical analyses allowed me to determine the quantity of the gases absorbed and given off in both cases.

Experiment CCXCIII shows that although before the compression the dog had consumed in a quarter of an hour 4.89 liters of oxygen and produced 2.99 liters of CO_2, after he had been taken from the apparatus in the same time he consumed only 2.02 liters and formed only 1.12 liters. Similarly, in Experiment CCXCIV, the consumption of oxygen fell from 3.95 liters to 2.15 liters, and the production of carbonic acid from 2.41 liters to 1.99 liters.

The decrease in the production of carbonic acid through the superoxygenation of the organism is indicated again by the study of the numbers listed in Column 8 of Table XV. If we examine Experiments CCLXXX, CCLXXXI, CCLXXXV, CCLXXXVI, CCLXXXVII, CCLXXXIX, CCXC, CCXCIII, we see that some minutes after the decompression we find in the blood only minimal proportions of carbonic acid. And this fact is all the more remarkable because, in the conditions in which the experiments were made, carbonic acid had been stored up in the blood in considerable quantity during the compression. Now when the animal was restored to the open air, this acid lessened to far below the normal proportion; in Experiment CCLXXXIX, it fell to 10.5 volumes per 100 volumes of blood, although its regular proportion, before the compression, was 44.5; in Experiment CCLXXXVI, the proportion before the compression being 43.0, it became 69.4 during the compression, and dropped to 9.9, 20 minutes after; in Experiment CCLXXXV, the same figures were 40.8, then 92.5, and finally 14.8.

It is quite clear then that, in consequence of the exaggerated superoxygenation of the organism, carbonic acid ceased to be produced in the tissues, and to pass into the blood, or at least that these phenomena were considerably slackened. This would have been manifest even during the compression, if I had been able to keep the animals in a current of compressed oxygen, to avoid the storing up of the carbonic acid due to the confinement. Furthermore, the experiments reported in Chapter II, in which we were dealing with pressures which were rather low but were made with almost pure air, showed, as we have noted, a diminution of the carbonic acid of the blood (See Table XII).

It appears from these data that the pulmonary ventilation would be capable of removing from the blood much more considerable proportions of carbonic acid than one would have thought, of almost exhausting, in a word, the bicarbonates and the phospho-car-

bonates, if the organism did not unceasingly furnish the venous blood with a constant source of this gas. We shall return to these data in another chapter, but it would be interesting to see, by a simple experiment, in which the same blood would be forced by a pump to pass constantly through the lungs, in which artificial respiration would be maintained, how much carbonic acid this blood could lose.

Before leaving this subject, let us say that the carbonic acid reappears but slowly in normal proportion in the arterial blood, when the superoxygenated animal recovers and lives. In Experiment CCLXXXIX, at the end of 1 hour and 15 minutes the proportion of carbonic acid was only 19.0; in Experiment CCXCIII, after 2 hours and 40 minutes, it had risen only to 26.5; but in Experiment CCLXXXI, at the end of 67 minutes it had returned to its original figure, 31.5. Let us note that this tendency to return to the normal proportion does not always indicate that the animal will survive, as Experiment CCLXXX shows.

Excretion of Urea. I now come to the urea. The experiments were conducted like those in the case of diminished pressure. The animal, subjected to a fixed diet for several days, was kept for several hours in compressed air, with a suitable current of air. The urine voided spontaneously or collected with a catheter in the preceding 24 hours was compared with that given in the 24 hours in which the compression took place. The account of the experiments will give the necessary details.

Experiment CCCVII. Dog weighing 12 kilos, eats every day at 7 o'clock in the morning a soup composed of 250 gm. of bread, 250 gm. of meat, and 500 gm. of water.

July 25, at 8 o'clock in the morning, catheterized the animal, which was then placed in a cage where the urine can be collected; he does not urinate, and July 26, at 8 o'clock, another catheterization gives 280 cc. of urine. This urine, analyzed by the Yvon process, gives 4500 cc. of nitrogen, that is, 12.1 gm. of urea.

July 26, from 9 o'clock to 3 o'clock, is subjected to a pressure of 8 atmospheres, under a current of air. Decompressed from 3 o'clock to 5 o'clock, is taken out in good condition. His rectal temperature is 35.5°.

July 27, at 8 o'clock in the morning (rectal temperature 35.7°) he is catheterized and the urine thus obtained is added to what he voided spontaneously. The total is 350 cc. of urine, which gives only 1398 cc. of nitrogen corresponding to 3.7 gm. of urea. I must add that the animal would eat only half his meal.

July 28, at 8 o'clock in the morning, catheterized again; there are 520 cc. of urine giving 3838 cc. of nitrogen, that is, 10.3 gm. of urea. During this day, the animal had absolutely refused to eat.

Experiment CCCVIII. Dog weighing 16 kilos; since July 31, eats every day 250 gm. of bread, 250 gm. of meat.

August 3, at 8:30, catheterized.

August 4, at 8:30, catheterized, and this urine added (100 cc.) to what was voided in the 24 hours (475 cc.) It gives, by the Yvon procedure, 8062 cc. of nitrogen, that is, 21.6 gm. of urea. Rectal temperature 35.8°. At 9 o'clock in the morning, placed in the apparatus, where the pressure rises to 8 atmospheres; decompression begun at 4:50, still under a current of air; the animal is removed from the apparatus at 6:20; he is in good condition; his temperature is 35.5°.

August 5, at 8:30 in the morning, the catheter drew 245 cc. of urine; there was none in the apparatus. It gave only 6329 cc. of nitrogen, corresponding to 16.9 gm. of urea.

These examples are enough to show that the chemical phenomena on which depend the formation of urea and analogous products are impeded in the same manner as those which determine the production of carbonic acid.

Sugar of the Blood; Glycosuria. A search for sugar in the blood and the urine shows us another chemical transformation, the destruction of this sugar, impeded by the action of oxygen under tension. In Experiment CCLXXXVI, the dog, which survived after convulsions of extreme violence, voided after the decompression urine with great sugar content; in Experiment CCLXXXI, which ended in rapid death, the few drops of urine which the bladder contained had high sugar content. This glycosuria, however, is not constant (Experiment CCXC).

Experiments CCLXXXV, CCLXXXVI, CCLXXXIX, CCXC, CCXCII, CCXCIII, and CCXCIV, that is, all in which the blood was tested for sugar, showed first that there is always much glucose in the arterial blood of a dog which has been subjected to compression. But as we always find glucose in arterial blood when it is treated according to the method of M. Cl. Bernard by boiling with sulfate of soda, comparative experiments CCLXXXIX, CCXC, CCXCII, CCXCIII, CCXCIV had to be made on the blood before and after compression, which showed very clearly that the latter contains more sugar than the former. Experiment CCXCIII proves besides that this excess of sugar disappears at the end of some time.

So the sugar which comes from the liver is much less rapidly broken down in the organism under the influence of compressed oxygen than at normal pressure, so that it is stored up in the blood to the point of producing glycosuria.

As to the production of the hepatic glucose itself, it is hampered by the sufficiently prolonged action of oxygen at high tension, as the following experiments prove.

Experiment CCCIX. March 7. Albino rat.

Rectal temperature 39.6°.

Kept for three hours in compressed air at 12 atmospheres, above a potash solution which absorbs the carbonic acid as it is formed.

Withdrawn suddenly, its rectal temperature is only 35.5°; it dies quickly with air in its heart.

Its liver does not contain sugar; much glycogenic material.

Experiment CCCX. March 15. Albino rat; rectal temperature 39.9°.

At 12 atmospheres of air for 3 hours, with potash.

Withdrawn; temperature 37.2°; dies like the rat in the preceding experiment.

No sugar in the liver.

In summary, consumption of oxygen, production of carbonic acid and urea, breaking down of glucose in the blood, all chemical phenomena which can be measured easily, appear to be considerably slowed down by the action of oxygen under high tension. And as these are the phenomena which determine the production of heat, it is not surprising to see that the temperature of the animals drops considerably. Nor is it astonishing to see that death is the consequence of such a depression in the intensity of the physico-chemical acts of nutrition.

But the violent excitation, the constant convulsions which accompany this death are still unexplainable by the depression alone; still less explainable is the persistence of the symptoms after normal pressure has been restored. In fact, in studying diminished pressure, we have noted a diminution of the chemical acts, analogous to what increased pressure revealed, and yet the convulsive struggling which precedes death by rapid decompression is in no way comparable to the violent convulsions due to oxygen and, furthermore, the return to free air marks irrevocably the end of all these symptoms.

This shows then that during compression the regular chemical acts of nutrition have been not only slowed up, but also modified; it is supposable that the result of this deviation has been the formation of some substance capable of playing a toxic part, a substance which, persisting after decompression, would continue to cause the symptoms and might bring on death, a substance the elimination or destruction of which would be necessary for a return to the state of health.

The chapter especially devoted to the study of fermentations will confirm us in this idea, and will even permit us to express it with more precision and clarity.

3. *Aquatic or Invertebrate Animals.*

The experiments reported up to this point were made only with vertebrate air-breathing animals: mammals, birds, frogs. It was interesting to study the action of oxygen at very high tension on invertebrate air-breathing animals and on aquatic animals.

Experiment CCCXI. April 25. Beetles, flies, caterpillars; centipedes; woodlice; arranged in two similar groups.

A. Placed in a corked flask; ordinary air, normal pressure.

B. In the compression apparatus, and taken to 6 superoxygenated atmospheres; the pressure falls to 2 atmospheres.

April 26. All alive except the flies in B.

Experiment CCCXII. May 12.

Lizard; golden beetles; carpenter bee, loaded with mites; drone, red fleas; flies; spiders; woodlice; centipedes.

At 5 o'clock in the evening, taken to 6 superoxygenated atmospheres.

May 13; 10 o'clock in the morning, decompressed.

The drone, the flies, the woodlice are dead, as are several red fleas; the others still move their feet a little, as does the carpenter bee.

The lizard has spontaneous and excitable convulsions; he dies some hours afterwards.

The beetles, the spiders, the mites, the centipedes are in good condition and survive.

Experiment CCCXIII. May 14.

Golden beetle, bees, ants, red fleas, wood fleas; flies; woodlice; spiders; snails; earthworms.

At 5 o'clock in the evening, placed in the cylindrical glass apparatus, with branches, earth, etc., to allow them to separate from each other. Taken to 5 superoxygenated atmospheres.

May 15, 2 o'clock. All dead except the spiders, the earthworms, which are twisted and intertwined, and the snails.

All die in the open air.

Experiment CCCXIV. May 16.

A capricorn beetle, 1 dragon fly, 1 blue butterfly, several bees, drones, ants, red fleas, flies, syrphus flies; centipedes, geophiles; woodlice; spiders.

At 11 o'clock in the morning; taken to 5 superoxygenated atmospheres; at 1 o'clock raised to 6; at 2 o'clock to 11 atmospheres.

Almost immediately all fall to the bottom, motionless, except the ants and the centipedes, which run up and down.

The flies die in a half hour at most.

4 o'clock; none of the insects are moving. Decompression made.

The bees, the flies, the syrphus flies, and the butterfly are dead.

The capricorn beetle, the dragon fly, the drones, the fleas, the ants, the woodlice are still moving a little.

The myriapods and the spiders are in good condition.

The next day, all are dead except the myriapods.

Experiment CCCXV. June 23.

Silkworm cocoons, sent by M. Raulin, from Alais, all of the same day.

A. 12 are placed in an open bell-jar.

B. 6 in the cylindrical glass apparatus, at 5 superoxygenated atmospheres.

C. (By some mistake, probably of the proof-reader, the conditions in C were not given; the pressure was probably much higher than in B. Translator.)

The air was changed every other day.

July 8. A. All have emerged.

B. No motion.

C. All dead; the skin of the chrysalises is not separable; they evidently were killed very soon.

So the formidable influence of compressed oxygen is felt by invertebrate animals as well as those belonging to the higher types.

The animals which in the simultaneous experiments first felt the fatal effects of oxygen were the flies; after them the bees and the butterflies; then the dragon flies and the fleas; considerably later, the ants and the coleoptera (longicorn and carabic). The woodlice, and especially the arachnids (spiders, acaridae) and the myriapods (centipedes, geophiles) are much more resistant. Then come the earthworms and the snails, at least for length of life, if not for lethal concentration.

The great importance of this kind of research is to show that death from excess of oxygen does not depend upon a mechanism peculiar to animals with red corpuscles, but is a general fact. There is present a profound modification in the metabolism of the tissues. We should note that these animals never seemed excited; on the contrary, they quickly become motionless and fixed in some corner of the apparatus, and die without showing any convulsion.

As a type of aquatic animal to be studied, I generally used young eels, called "de la montée", the hearts of which one can easily see beating.

Experiment CCCXVI. April 1. Small eels "de la montée", transparent, temperature 15°.

A. 5 are placed in a well-corked test tube;

B. At three o'clock, 5 are placed in the cylindrical apparatus and raised to 11 atmospheres of an air with 50% of oxygen. Oxygen tension 550, corresponding to about 26 atmospheres of air.

In the evening at 7:30, nothing particular apparent.

April 2, 1 o'clock. A: in good condition.

B: dead, stiff, not transparent, and not contractile when stimulated electrically.

Experiment CCCXVII. April 2. Similar eels.

A: these are the same ones as A of the preceding experiment.

B: at 3 o'clock, 5 are placed in the apparatus at 5½ atmospheres of air with 57.5% of oxygen. The tension is therefore 316, corresponding to 15 atmospheres of air.

April 3, 10 o'clock in the morning; A, very lively; when quiet, respiratory rate 78 and pulse 40.

B: move when the apparatus is shaken, but not spontaneously. Pulse 20 at the most; respirations, when eels are quiet, are not visible; after they were shaken, I counted 22. From time to time, violent struggling.

6 o'clock in the evening; in convulsions and are twisted in the shape of an 8.

April 4, 1 o'clock. B: all dead, opaque.

Experiment CCCXVIII. April 4. Similar eels.

A: These are the eels of the two preceding experiments.

B: at 4 o'clock, 5 are placed under pressure of 10 atmospheres of air.

April 5, 9 o'clock in the morning: A: very lively, 66 very ample respirations; pulse 26.

B: at the bottom of the apparatus, hardly moving; respirations invisible; pulse 20.

April 7. Same, all living; rapid decompression.

Experiment CCCXIX. July 8. Eels, not transparent.

At 5 o'clock in the evening, under compression of 10 atmospheres of air containing 50% of oxygen; the apparatus is shaken to saturate the water containing the eels.

July 9, 1 o'clock; all dead, opaque.

I tip the apparatus so that not the air but the water will escape; this water, when collected in the syringe, froths, and is taken to the mercury pump.

It contains 14 volumes of oxygen per 100 volumes of liquid, and the same quantity of nitrogen.

Much weaker pressures are enough to kill aquatic animals when their action is continued long enough.

Experiment CCCXX. May 20. Frog tadpoles, several days out of the egg and in very good condition in the laboratory.

A: 5 in a little corked flask, with water, at normal pressure.

B: 5 in a flask with water, all in the glass compression apparatus, at 7 atmospheres of air.

May 22: all living.

May 24: all living in A, all dead in B, probably since the day before.

Experiment CCCXXI. May 24. Same experiment, with similar animals; 7 atmospheres of air.

May 27; all the tadpoles in the compressed air are dead.

So aquatic animals are killed like air-breathing animals, when

oxygen is dissolved in the water in sufficient quantity. A pressure of 15 atmospheres kills them quickly and they cannot live in 7 atmospheres. The transparency of the eels allowed us to note a considerable slowing down of the heart beats, while the respirations weakened so as to be almost invisible.

In another part of the book we shall draw conclusions from these last experiments from the point of view of the physics of the earth. It is enough here to note the generality of the fatal action of compressed oxygen, which acts upon warm-blooded animals as well as upon cold-blooded animals, upon vertebrates and invertebrates, upon animals which live in the water and those which breathe air, upon adult animals and those in the process of development. Chapters V and VI will permit us to extend this formula to plants, to ferments, in a word, to every living thing.

Subchapter V
SUMMARY

As a result of these numerous experiments, we are now in a position to state the first cause of the death of animals and plants subjected to a fairly high oxygen tension. Let us set aside the violent convulsions displayed by the higher animals and go to the bottom of the phenomena.

Life is only the result of a complex and harmonious combination of chemical changes belonging to the group of fermentations; some are due to the direct intervention of the formed elements of the body; others are the consequence of the action of unstable and soluble substances, like diastase, previously formed by the action of the formed elements. In the interior of each of the anatomical elements the vital activity is maintained only by the action of these substances which are created, act, are transformed, and are destroyed there.

But that life may be maintained, the multiple phenomena must *go on with constant regularity, or rather harmony.* When their intensity alone is modified, without their relations being altered, vital activity decreases, sometimes is even halted, possibly for a long time, and then reappears when more favorable conditions occur. This happens through cold, through desiccation, and, to return to our subject, through decreased pressure. Seeds, preserved intact in a vacuum, germinate when returned to the air; meat, which has remained fresh in a vacuum, decays when oxygen restores activity to its vibriones.

When, on the contrary, it is not merely the quantity, but also the quality of the chemical changes that is altered, symptoms appear, the details of which are far from being known and which have such consequences that even if normal conditions are restored, the vital activity is not resumed. This happens through heat, through excessive moisture, and through increased pressure. Seeds kept apparently intact in compressed air do not germinate when returned to normal pressure, and it is in vain that oxygen at its usual tension comes in contact with the definitely dead vibriones which swarmed upon the meat previously subjected to compressed oxygen.

We do not need to go as far as death to show these important differences. An animal subjected to decompression is seized, at a certain moment, by convulsions, which a return to normal pressure checks immediately: *Sublata causa, tollitur effectus* (If the cause

is removed, so also is the effect). But the convulsions due to excessive pressure continue even when the apparent cause has been removed; that is because the real cause, the chemical change, still exists, still operates, and excites the nervous centers.

Under the influence of oxygen at high tension, within the interior of the anatomical elements, either isolated in individual cells or grouped in tissues, chemical alterations take place, which produce lasting substances, the presence of which disturbs the harmony necessary for the continuance of life, in the element first, then in the complex being.

These are, indeed, rather vague terms, but this vagueness results from the general condition of science and should not be made a reproach against me. What do we know about the molecular transformations which take place regularly in the tissues and in the interior and on the surface of the anatomical elements? The little knowledge we have I have subjected to experimentation; I have seen that the transformation of starch into glucose, that the reduction of glucose into its primary elements are delayed by oxygen under high tension. Now these are general acts which appear, we know, in the life of a mycoderm cell, as in the cell of a mammal or a bird. They are delayed, but yet the soluble ferment which produces them is not altered at all, and will resume all its activity later, at normal pressure. Why then, after this return to normal pressure, does not life reappear, as after the suspension due to a vacuum or to cold? Can it be that the ferment, whose regular action has diminished, has acquired a new one, which has produced this lasting substance the origin of which we are seeking? Has the fermentable matter, on the contrary, changed so that now it withstands the action of the preserved ferment?

It is very difficult to answer these questions today. All that I can say is that the substances subjected to compression: meat, eggs, milk, and bread, soon give an acid reaction, due probably in part to lactic acid. It is not impossible that the presence of this acid in the interior of the anatomical elements is the cause of death.

But without discussing any longer phenomena the inner significance of which we cannot explain, we are justified by the numerous experiments, the report of which has filled so many pages, in saying that, under the influence of oxygen at high tension, within each anatomical element chemical alterations take place which are incompatible with the life of this element. When this is granted, all the varied phenomena which we have enumerated are easily connected and explained.

Are we dealing with a living being reduced in its elementary structure to a single cell or a small number of cells? Since its vital activity is generally manifested to us by phenomena known by the name of true fermentations (alcoholic, acetic, lactic, and putrefactive), its death will result in the permanent stoppage of these phenomena, unless new ferments are sowed.

Or, to go at once to the opposite extreme, are we dealing with an animal which is very complex in its structure? The anatomical elements which form its tissues are threatened with death. Those among them which in biochemistry played the part of formed ferments cease to act, or lose energy of action. The phenomena of zymotic fermentation which take place both without and within them lose intensity and degenerate. Their personal qualities, their contractility, their power of transmitting stimuli or of changing them into reaction become modified and tend to disappear.

Hence come the general lessening of the chemical phenomena of life; the decrease in oxygen consumption, in carbonic acid production, and in excretion of urea; the appearance in the urine of sugar which is no longer sufficiently broken down; and finally, an enormous lowering of the temperature.

And at the same time,—since whenever a great and rapid disturbance affects the equilibrium of the functions of a higher animal (hemorrhage, asphyxia, etc.), it is the central nervous system which, as it is the first to be stimulated, shows by its violent reactions the danger which threatens the whole organism,—there appear these convulsions which give evidence by their persistence after a return to normal pressure that a profound chemical change has taken place in the tissues of the spinal cord or in the blood which supplies them and would thus bring them a kind of poison. Last come the muscular contractions modified in their behavior, like cramps, such as occur in every dying muscle.

Between these two extremes, the isolated cell and the warm-blooded vertebrate, all the intermediaries: on the one hand, molds, algae, seeds, vascular plants; on the other, annelids, mollusks, insects, fish, reptiles. The whole aggregation of living beings, in a word, dies absolutely when the oxygen tension rises high enough. Not one, we can affirm, would withstand a tension corresponding to the pressure of 20 atmospheres of air. We shall return to the inferences suggested by this unexpected phenomenon.

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[1] See my *Mémoire sur la vitalité des tissus animaux* (*Annales des sciences naturelles. Zoologie*, 1866).

[2] Paul Bert. Note on a certain sign of approaching death in dogs subjected to rapid blood-letting (*Mémoire de la Société des sciences de Bordeaux*, Vol. IV, p. 75, 1866).

[3] Contributions to the study of venoms: scorpion venom. *Comptes rendus de la Société de biologie pour* 1865, p. 136.

[4] See the discussions of MM. Davaine, Jaillart, and Leplat: *Comptes rendus de l'Académie des sciences*, Vol. LXI, 1865.

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OXYGEN POISONING IN MAN

BY

KENNETH W. DONALD, *D.S.C.*, M.D., M.R.C.P.

Late Senior Medical Officer, Admiralty Experimental Diving Unit; Chief Assistant, Medical Professorial Unit, St. Bartholomew's Hospital

PART I

The recent war greatly stimulated the study of human tolerance to various changes in environment. This article confines itself to tolerance to increased tensions of oxygen, though there are other important factors at increased pressures which are not considered here. At sea-level there is an oxygen tension of about 159 mm. of mercury, and this is the maximum oxygen tension encountered in any natural environment. The oxygen tension in the tissue spaces of warm-blooded animals is from 20 to 40 mm. of mercury. In under-water work man, by means of various appliances, breathes gases at the pressure to which he is exposed, this being the first essential of prolonged under-water existence. The second essential is that his respiratory movements must continue within their normal range and with their normal frequency. The third is that the gases to which he is exposed must not be noxious, either at the time of exposure or on returning to normal atmosphere. Under most operational conditions it is preferable that the diver is self-dependent and carries his respiratory gases with him. If he carries air, then this must be expelled from his apparatus after each breath and there is great wastage and exposure to dangerous tensions of nitrogen. If he carries oxygen, this gas can be employed not only for metabolic purposes but for the essential rinsing of the lungs during respiratory movement. Thus no gas is wasted and maximum endurance for a minimum load is possible. It would appear, therefore, that oxygen is the ideal gas for this purpose, provided it is devoid of toxic effects. It is almost certain that the tissues of man, when breathing oxygen at increased tensions, are exposed to an internal environment which has been previously unknown to living matter, and it is therefore difficult to postulate what the reaction to such tensions would be. Whales, in deep dives, protect their general tissues by the complete collapse of their relatively small lungs and transfer of the gases to the inactive dead space.

The first important contribution to this subject was made by Paul Bert in 1878. His pioneer work has withstood the test of time in a most impressive manner. He showed that oxygen at increased pressures was highly poisonous and that no living matter was exempt. Larks exposed to 15–20 atmospheres of air convulsed and finally died. In a large series of experiments Bert showed that the oxygen tension was the decisive factor in the immediate effect of air or of any mixture of nitrogen and oxygen. Lorrain Smith (1899) next demonstrated that animals breathing oxygen at moderately high tensions over prolonged periods suffered severe and finally fatal pulmonary damage. An enormous amount of animal experimentation followed, but "L'effet Paul Bert" (convulsant) and "L'effet Lorrain Smith" (pulmonary irritation) remained the cardinal features of oxygen poisoning.

With regard to human experiments, the first recorded were by Bornstein and Stroink (Bornstein, 1910; Bornstein and Stroink, 1912), who breathed oxygen for 45 minutes at 3 atmospheres absolute (ats. abs.) in the Elbe tunnel without ill effect. In 1912 Bornstein suffered from clonic spasm of the legs while riding an ergometer under similar conditions for 51 minutes. In 1930 the late Dr. J. S. Haldane (Haldane and Priestley, 1935) reported confusion and amnesia in deep-sea air divers at 300 ft. (91.4 m.), and these symptoms were attributed to the raised tension of oxygen. These effects were proved by Behnke *et al.* (1935) to be due to the intoxicant effect of nitrogen at high pressures. Yet as a result of this misconception diving on pure oxygen was limited in the Royal Navy to 2 ats. abs. (apart from submarine escape). In 1933 two Royal Naval officers, Damant and Phillips, breathed oxygen at 4 ats. abs. in compressed air. Convulsive symptoms occurred in 16 and 13 minutes respectively. Phillips suffered a major convulsion after being turned on to air but while still at 4 atmospheres pressure (Thomson, 1935). In 1934–6 Behnke and co-workers carried out a series of human experiments. Only two exposures were made at 4 atmospheres, where one subject suffered acute syncope after 43 minutes. The other subject convulsed after 44 minutes. At 3 atmospheres four subjects breathed oxygen for three hours with no demonstrable ill effect. In a second series at this pressure the experiment was continued into the fourth hour, when three subjects suffered abrupt onset of vertigo, nausea, and a sensation of impending collapse. Concentric contraction of the visual field was also demonstrated. These results were published and obtained widespread recognition and acceptance. Throughout the world it was assumed that men at comparative physiological rest, as in these experiments, were safe breathing oxygen for at least 30 minutes at 4 atmospheres, and for at least three hours at 3 atmospheres. In time even the proviso concerning rest was usually omitted. The British finding appeared to have

been unnoticed, or forgotten, even in Great Britain. In 1941 J. B. S. Haldane reported a convulsion after breathing oxygen for under five minutes, at a pressure of 7 ats. abs., during experiments related to the *Thetis* disaster.

The investigations of oxygen poisoning described here were started in April, 1942, owing to the occurrence of several cases of unconsciousness in oxygen-breathing apparatus at depths and in times which were then considered to be safe. The Admiralty Experimental Diving

FIG. 1.—Subject breathing oxygen under pressure.

FIG. 2.—Soft-helmeted counter-lung oxygen-diver. (Human torpedoes.)

[Admiralty Photos.

Unit was created to investigate this and other urgent problems of high-pressure physiology. The main body of human experiments described in this article were carried out between June, 1942, and February, 1943. No experimental dives where men had breathed pure oxygen at toxic tensions under water had yet been reported. The object of these experiments was to gain a more comprehensive picture of oxygen poisoning in the human. Large groups of subjects were therefore employed, and over 2,000 experiments were carried out. Great care was taken to avoid an heroic or "Jules Verne" atmosphere.

The Marked Variation of Oxygen Tolerance in Man

The first series of experiments to be carried out was to determine the oxygen tolerance of a group of healthy male subjects at a fixed oxygen tension (3.7 ats. abs.). This series was carried out in a pressure chamber of 100 c. ft. (2.83 m.³) capacity. The subject was seated opposite two observers who were in telephonic communication with those outside. All subjects breathed oxygen at pressure until acute symptoms occurred. Experiments in compressed air have a number of advantages. The subject's state can be easily observed and subjective end-points are less likely. Convulsions are a lesser risk. Oxygen was breathed from a Siebe Gorman "salvus" apparatus. Efficient rinsing out of the subject's lungs was carried out and repeated frequently. A series of analyses, however, showed that even with this regime it was difficult to maintain a concentration higher than 95% of oxygen. In most exposures the pulse and respiratory rates were noted every five minutes. Subjects varied from cooks to recently trained divers, experienced divers, submarine ratings, medical officers, special service operational personnel, and mine-disposal officers and ratings. All were Grade A1 in fitness, and ages varied from 18 to 40 years. Experiments carried out in this manner are referred to hereafter as in the "dry," in contrast to those carried out under water and referred to as in the "wet." The results of these experiments are given in Table I and shown graphically in Fig. 4 (in the "dry").

TABLE I.—*Oxygen Poisoning at 90 ft. (27.4 m.) in the Dry in 36 Subjects in Order of Performance*

Exposure (mins.)	Symptoms	Exposure (mins.)	Symptoms
96	Prolonged dazzle; severe spasmodic vomiting	18	Vertigo and severe lip-twitching
67	Severe lip-twitching	18	Vertigo + +; epigastric aura
62	Euphoria and lip-twitching	17	Lip-twitching
62	Nausea and vertigo; arm twitch	17	Lip-twitching; spasmodic respiration
54½	Severe lip-twitching	17	Lip-twitching; spasmodic respiration
51	Dazzle and lip-twitching	16½	Slight lip-twitching
50½	Blubbering of lips; fell asleep	16	Severe lip-twitching; spasmodic respiration
50½	Dazed and lip-twitching	15½	Inspiratory predominance; lip-twitching and syncope
34½	Nausea, vertigo, lip-twitching	15	Nausea, syncope, and confusion
33	Convulsed	14	Lip-twitching
32	"	12½	"
32	Severe lip-twitching	9	Dazed and lip-twitching; paraesthesiae
30	Convulsed	9	Lip-twitching and vertigo
26½	"	7½	Severe lip-twitching
25½	Drowsiness and lip-twitching	7	"Diaphragmatic spasm"
24½	Severe lip-twitching	6	Severe nausea
23	Lip-twitching; epigastric aura	6	Severe lip-twitching
20½	Lip-twitching; twitch L. arm; amnesia		
19½	Convulsed		

Out of 36 subjects five convulsed, the rest recovered on being turned on to air. The most striking finding was the enormous variation in oxygen tolerance in a group of human beings. Exposures causing marked symptoms at this tension varied from 6 to 96 minutes. The tolerance of each subject was unpredictable. Many attempts to correlate tolerance with age, height, weight, physical fitness, athleticism, smoking, ingestion of alcohol, psychological health, or personality assessments all failed. Symptoms will be discussed in detail later.

The times of exposure causing acute symptoms show a skew type of distribution, notable examples of which are

the response of animals and insects to drugs and hormones. It is clear that the previously reported times of safety at this pressure were dangerously incorrect; in addition, no allowance had been made for individual variation, which is found to be over an enormous range.

Oxygen Tolerance under Water

It has already been emphasized that up to the beginning of these investigations all experiments regarding oxygen tolerance had been carried out by subjects in dry chambers. A series of dives was initiated to discover whether man's tolerance under water was similar to that so far determined in compressed air. The experimental arrangements can be seen in Fig. 3, which is self-explanatory. The respiratory apparatus was a modification of the Davis submarine escape apparatus adapted for four hours' endurance. A light rubberized canvas suit with a soft helmet was worn. The diver was submerged in an open tank and tested for leaks; he then walked to the high-pressure tank and was lowered into the water. The upper hatch was closed and air pressure rapidly applied. The diver was thus exposed to the increased pressure but was under water. On the average, subjects were breathing oxygen, mostly at atmospheric pressure, for ten minutes before arriving at the appropriate experimental depth. Time of compression averaged 90 seconds. The temperature of the water was maintained at 65° F. (18.3° C.). As the depth reading was of the air pressure above the water, the oxygen was breathed at an additional 3 ft. (0.91 m.) of water pressure (see Fig. 3).

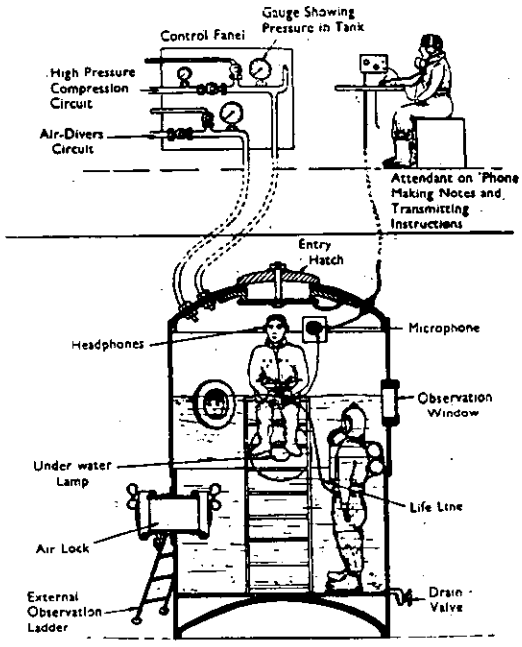

FIG. 3.—Showing wet pressure chamber with diver under water breathing oxygen in self-contained set. Internal and external attendants.

The first series of dives was to 50 ft. (15.2 m.) (2.5 ats. abs.) and the time limit was 30 minutes. One hundred different subjects were employed. If the diver convulsed or had severe symptoms he was hauled out of the water and turned on to oxygen. The mouthpiece acted as an excellent gag during convulsions, and attendants were taught to maintain a good airway. Out of these 100 subjects 26 convulsed, 24 had symptoms, and 50 had no symptoms. Space does not allow details. According to previously accepted figures men were safe breathing oxygen at this depth for at least two hours. The great variability, already demonstrated, makes hard-and-fast rules impossible, but, even allowing for this variation, it was strongly suggested that there was a marked decrease of average tolerance compared with that obtaining in the experiments in compressed air.

A series of dives was therefore carried out to compare the tolerance of subjects in compressed air, and under water, at 60 ft. (18.3 m.) and 90 ft. (27.4 m.) pressure of sea-water. In the first series six subjects were employed. At 60 ft. in the "dry" the subjects tolerated oxygen-breathing for 180, 120, 120, 158½, 101, and 51 minutes, in the first three cases without symptoms. At the same pressure under water the same subjects experienced acute poisoning in 76, 37½, 25, 61, 19, and 12½ minutes respectively. At 90 ft. their performances in the "dry" were 51, 54½, 62, 34½, and 32 minutes, whereas under water they survived only 12, 11, 25½, 18½, and 9½ minutes respectively (one subject indisposed in this series). All these exposures at 90 ft. were terminated by acute symptoms. A larger series of "wet" and "dry" experiments at 90 ft. is shown in Fig. 4. It will be seen from these results that oxygen

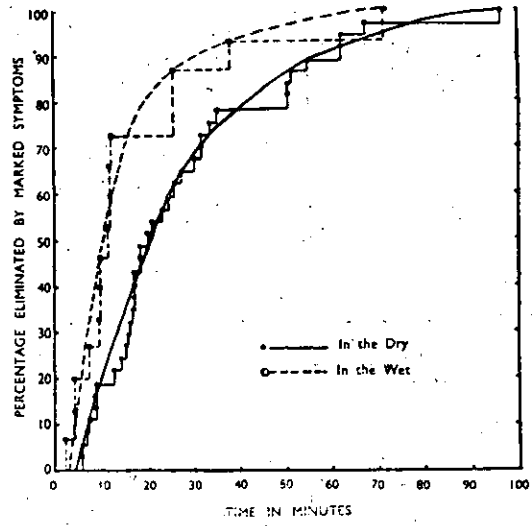

FIG. 4.—Percentage of subjects eliminated by toxic symptoms at 90 ft. (3.73 ats. abs.) breathing oxygen in compressed air and under water (65° F.) in diving-suit. No work performed.

tolerance is greatly decreased when the subject is under water. The enormous importance of this finding need hardly be pointed out. The causes of this impairment remain unknown. There is the added 3 ft. (0.91 m.) of pressure already mentioned, and the diver is breathing pure oxygen in contrast to 95% approximately in the "dry." These two factors are quite inadequate to explain the phenomenon completely. Carbon dioxide accumulation was suspected, as this is known to increase susceptibility to oxygen poisoning in animals (Hill, 1933). Numerous gas analyses negated this possibility. The lack of a rigid helmet, respiratory resistance, the bandaging effect of the suit, the diver's posture, and hydrostatic effects have all been investigated with negative results.

Time–Pressure Relationship for Men Breathing Oxygen Under Water

Next an attempt was made to plot individual curves expressing the relationship of time of survival to pressure. In view of the individual variation it was realized that each diver would have a different curve of tolerance. After a large number of experiments a new factor became increasingly manifest. The tolerance of individual subjects varied from day to day, and it was quite impossible to plot a curve for a single individual. Certain subjects showed this individual variation to a greater degree than others. As with the variation between individuals, no cause for this varying susceptibility to oxygen poisoning could be discovered. In view of these findings, a subject of apparently good resistance was chosen. He dived twice a week over a period of three months to a constant depth of 70 ft. (21.3 m.) in the "wet" (3.12 ats. abs.). He wore the same suit and apparatus on all occasions. All dives were carried out about 11 a.m., after an early and light breakfast. His end-points were usually very definite and his health excellent throughout. The results are given in Table II with end-points and

TABLE II.—*Tolerance of a Single Diver at 70 ft. (21.3 m.) in the Wet over a Period of 90 Days*

Day in Series	Time (mins.)	Symptoms
1	7	Lip-twitching +
7	12½	Nausea +
9	86	Auditory hallucinations, lip-twitching
15	27	Lip-twitching +
17	23	" +
20	21	" +
30	28	" +
34	61	" +
37	148	Feeling "cross-eyed"; lip-twitching
42	37½	Lip-twitching; coughing
44	96	Lip-twitching; stertorous breathing
48	31½	Lip-twitching +
56	67½	Lip-twitching
70	62½	Lip-twitching; tinnitus; choking sensation; gasping; confusion
72	43	Lip-twitching +
76	41½	Lip-twitching; vertigo; dazzle
78	82	Lip-twitching; dazzle; dyspnoea
80	29½	Lip-twitching; nausea
83	125	Dazzle; amnesia
90	78	Nausea; severe lip-twitching

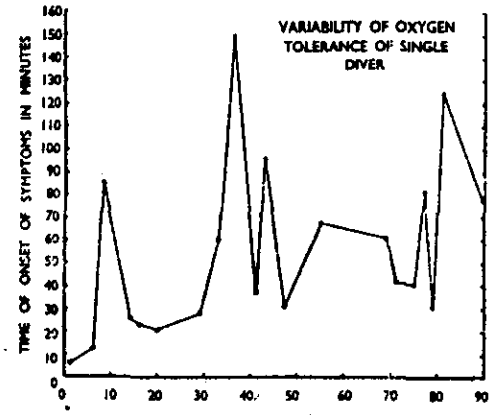

FIG. 5.—Time of exposure causing toxic symptoms in same diver as Table II under sea-water at 70 ft. (65° F.) plotted over a period of 90 days. *No work performed.*

in Figs. 5 and 6. The curve of distribution obtained was very similar to that showing variation of tolerance in a group. Statistical analysis showed that this subject had a greater variance of toleration than the average. A larger series of experiments confirmed this individual variation. Good examples, in one series, were those divers who survived 100 minutes under water at 50 ft. (15.2 m.). The averages of all their other performances at this depth were 22, 19, and 15 minutes. One subject, who convulsed after 12 minutes at 50 ft., completed 100 minutes at 50 feet

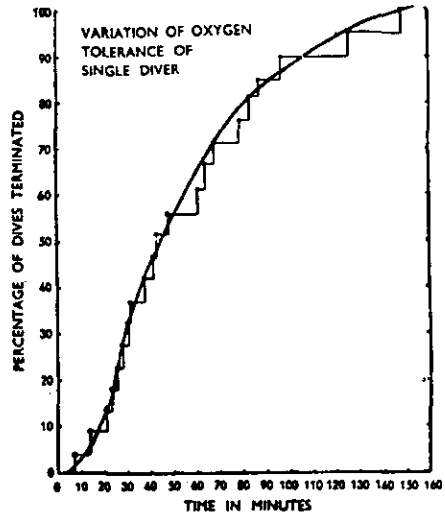

FIG. 6.—Percentage of dives terminated owing to toxic symptoms as a function of duration of exposure. Depth throughout, 70 ft. of sea-water (65° F.). Dives over a period of 90 days. No work performed.

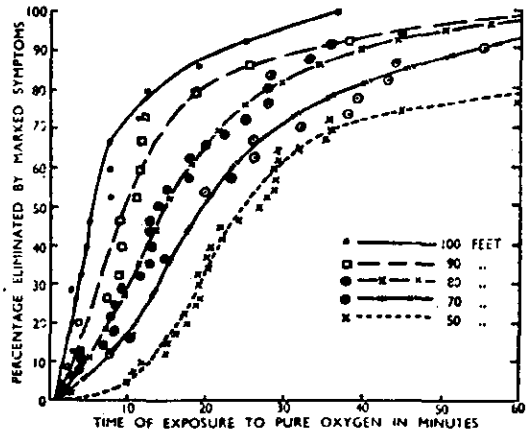

FIG. 7.—Percentage of divers on oxygen, under water, surviving at various times up to 1 hour at 50 ft., 70 ft., 80 ft., 90 ft., and 100 ft. of sea-water, 65° F. throughout. No work performed. Actual end-points plotted.

without symptoms 16 days later. Six days after this he again convulsed at 50 ft. in 32½ minutes. Such findings make it clear that to dive on oxygen to any toxic pressure involves a risk that it is impossible to assess, even if the diver's tolerance has been previously determined.

It now became apparent that the only satisfactory method of assessing oxygen tolerance at various pressures was to employ groups of men for each pressure. Dives were

carried out in the "wet" to a definite end-point by groups of subjects at 50, 60, 70, 80, 90, and 100 ft. in an attempt to obtain a clear overall picture. The results are shown in Fig. 7. The increased toxicity as the depth becomes greater is clearly shown. The highly skew distribution conforms satisfactorily with the Galton-MacAlister law, and it can be demonstrated that all curves in Fig. 7 are the same curve. In other words, the variability of the group is independent of the depth. The coefficient of variation has the huge values of 76–109%, as compared with about 3–4% for such human characters as height, arm length, and alveolar carbon dioxide level. Even more remarkable is the fact that a single diver gave a graph (Fig. 6) of the same type with a coefficient of variation of 67%. This means that a single man may be almost as variable as a group, though this is exceptional. Statistical analysis shows that only 40% of the total variation of oxygen divers is accounted for by day-to-day variation of each individual diver. The other 60% is due to variation between the averages of the different divers.

Maximum Non-toxic Depth under Water at Rest

Next an attempt was made to discover at what pressure, under water, oxygen ceases to cause toxic nervous symptoms that would make free diving dangerous. As work is generally known to impair tolerance the investigation was first carried out without exercise. A large number of dives for a maximum of two hours was performed, and toxic symptoms, and even convulsions, were encountered at 40 ft. (12.2 m.), 35 ft. (10.7 m.), and 30 ft. (9.1 m.). The results may be summarized as follows:

Depth (feet)	No. of Subjects	No. with Symptoms	No. Convulsing
40	29	15	4
35	21	6	1
30	20	3	2
25	28	0	0

It is possible that longer exposures may have caused symptoms at 25 ft. (7.6 m.), but this period is longer than any practical dive on oxygen to this depth. It must be remembered that these divers were exposed to a pressure of oxygen that would occur with a sounding of 32 ft. (9.7 m.). It is a most surprising finding to obtain oxygen convulsions at as low a pressure as 33 ft. (10.1 m.) of sea-water (2 ats. abs.). At such a tension the oxygen dissolved in the blood plasma is inadequate for even basal metabolic requirements, and the haemoglobin is still being actively employed for oxygen transport. Gesell (1923) had suggested that the deactivation of the haemoglobin cycle rendered this substance unavailable for carbon dioxide transport from the tissues and that this caused a severe tissue acidosis. Campbell (1930), by his nitrogen injection technique, had confirmed that there was a remarkable rise of tissue carbon dioxide tension at the usual convulsant levels employed in animal work. However, at the minimal tension causing convulsions in these experiments the carbon dioxide tension was shown by Campbell to be hardly raised. It would appear, therefore, that accumulation of carbon dioxide in the tissues is not the essential cause of oxygen convulsions; and this is in accord with more modern research, which will be discussed later.

Effect of Work on Oxygen Tolerance

It has been generally accepted that work diminishes tolerance to oxygen at increased tensions. However, no reliable experimental data are available. *Il Polombaro* (Italian Ministry of Marine, 1938) gives tables showing a marked effect of work, but these figures appear to be entirely theoretical. A further programme of experimental exposures was therefore carried out in the "wet" with hard work. Controls with the diver resting were also performed. Subjects worked vigorously by lifting a large bag of weights by pulley. Dives were carried out at 50, 40, 35, and 25 ft. These experiments showed conclusively that oxygen tolerance is markedly diminished by work. Figs.

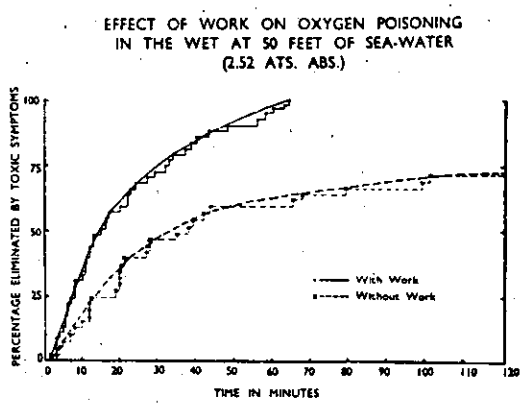

FIG. 8.—Percentage of divers eliminated by toxic symptoms at 50 ft. in the wet (2.52 ats. abs.) during a period of 2 hours, with and without work: 46 divers working, 41 not working. Temperature throughout, 65° F.

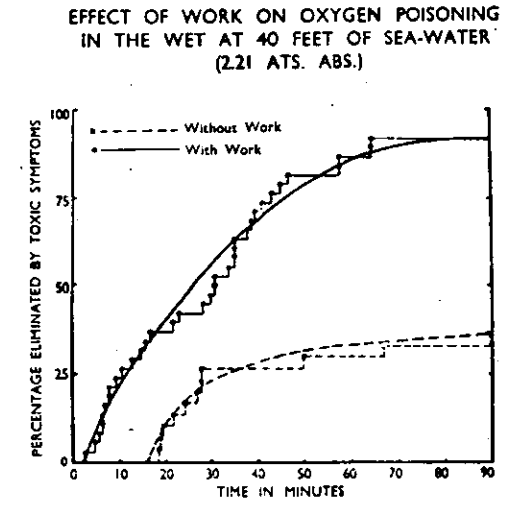

FIG. 9.—Percentage of divers eliminated by toxic symptoms at 40 ft. in the wet (2.21 ats. abs.) during 90 minutes, with and without work: 39 working, 31 not working. Temperature throughout, 65° F.

8 and 9 show the results at 50 ft. and 40 ft. with and without work. Even at 25 ft. toxic symptoms occurred in five out of 18 subjects, though no convulsions were recorded.

The physiological reasons why work reduces oxygen tolerance are not at present definitely known. A further increase of carbon dioxide in the tissues is an obvious possibility, though more reduced haemoglobin is available for carbon dioxide transport. The rise of alveolar carbon dioxide, which is probably very marked when exercising on pure oxygen (to be discussed in later publications), presumably causes cerebral vasodilatation, which may be another adverse factor.

Effect of Temperature on Oxygen Poisoning

Previous work had indicated that the lowering of the environmental temperature increased the oxygen tolerance of small experimental animals (de Almeida, 1934.; Campbell, 1937). Three series at 50 ft. were performed, at 87.5° F. (30.8° C.) (steam-heated), at 45° F. (7.2° C.) (ice-cooled), and control exposures at 65° F. (18.3° C.). Divers were allowed to vary their underwear under the suit as the application of this work to operational problems was the first consideration. It is doubted if these expesures could have been tolerated without this variation in clothing. No exercise was carried out. This was advantageous at a higher temperature but disadvantageous to the diver in cold water. The divers complained bitterly of the cold and found the heated dives equally uncomfortable. These experiments showed that oxygen tolerance was equally affected by heat and cold. Although the performances below 30 minutes were only slightly impaired all outstanding performances were eliminated. It is possible that this delayed effect was due to changes in body temperature, as symptoms suggested that this occurred after about 20 minutes.

[To be concluded, with a bibliography, in next week's issue.]

OXYGEN POISONING IN MAN

BY

KENNETH W. DONALD, *D.S.C.*, M.D., M.R.C.P.

Late Senior Medical Officer, Admiralty Experimental Diving Unit; Chief Assistant, Medical Professional Unit, St. Bartholomew's Hospital

PART II

Signs and Symptoms of Oxygen Poisoning

The available knowledge of the signs and symptoms of oxygen poisoning in man at the beginning of these experiments was extremely scanty. Only about 12 separate exposures where acute toxic symptoms had occurred had been described. It is not certain that Bornstein suffered from oxygen poisoning (see below). All these experiments were in compressed air, and with the exception of Bornstein all subjects were seated and at comparative physiological rest. The British Naval instructions at this time (1941) read as follows: "Symptoms: Tingling of the fingers and toes and twitching of the muscles, especially round the mouth (warning symptoms). Convulsions followed by unconsciousness and death if a remedy is not taken." The U.S. Naval instructions stated: "The first signs of oxygen toxicity are the flushing of the face, nausea, dizziness, and muscle-twitching. A feeling of being irritable and a sense of excitement may follow. As the pressure is increased nausea, vertigo, and, finally, unconsciousness and convulsions ensue."

It was inevitable, with the limited data available, that these instructions were brief and not altogether accurate. Tingling of the fingers and toes had not been reported in any experiment, but was inferred from its occurrence in the aura of idiopathic epilepsy. In the first large series of human experiments, described in this article, a more complete picture of the syndrome of oxygen poisoning in the human has resulted. Most of the signs and symptoms described in the pre-convulsive stage, in the auras, or in the non-convulsant equivalents of epilepsy have been encountered. As in that disease, the total of signs and symptoms is now known. Yet—again as in epilepsy—the individual pattern of signs and symptoms varies enormously within this framework. Signs and symptoms as experienced when the subjects were breathing pure oxygen in compressed air are first described, as the subjects' environment was more normal and careful direct observation was possible.

Facial pallor usually occurs a few minutes after the beginning of the exposure. It varies from person to person in degree and time of onset. The degree of facial pallor is in no way indicative of the subject's sensitivity or of an impending end-point. Fasciculation of the lips or face is often seen early in the experiment and intermittently throughout the exposure. This has been partially attributed to fatigue caused by the mouthpiece and a not unnatural nervous tension. It is a common occurrence when patients

are breathing from a spirometer for B.M.R. estimations. Fasciculation frequently appears in muscles which later show severe and sustained twitches, and it is undoubtedly increased by breathing oxygen at increased tensions. A number of subjects show facial perspiration varying in degree from fine beads to literal pouring. Generalized perspiration is infrequent, and is usually associated with the occurrence of more acute symptoms. Salivation seems to be increased (as in animals), but some is undoubtedly reflex from the irritation of the mouthpiece, and is therefore difficult to assess. Almost all the subjects appear to be under stress even though they have no specific symptoms. These are all early findings, and the subject will continue without further event for varying times according to his tolerance.

The next group of symptoms to be described may be classified as minor crises in so far as they are usually transient and the subject is able to continue breathing oxygen. The subject may complain of nausea, vertigo, malaise, apprehension, or choking sensations. Intermittent lip-twitching of a slight or moderate degree or an increase in the frequency of respiration may be noted by the observer. Palpitations, involving an awareness not only of the action of the heart but of arterial pulsation throughout the body, may cause the subject considerable discomfort. These disturbances may last for only a few seconds to a few minutes, and the subject finally resumes his former symptomless state and may continue the exposure for a considerable time before an acute end-point. The course of these minor crises is unpredictable, and the observer has to be constantly on the alert for a sudden exacerbation with danger of convulsion. Other subjects have no such transient episodes, but first experience pronounced symptoms shortly before or at the end-point.

Finally, a group of symptoms occur which, although not demanding immediate cessation of the exposure, signify that intoxication is becoming more intense and that acute symptoms will not be greatly delayed. There may be pronounced mood changes with depression or euphoria. Severe irrational apprehension, sometimes amounting to acute terror, may be experienced. Alternatively, the subject may feel "far away" or experience complete indifference to his surroundings. Others are somnolent, and in one case the subject fell into a deep sleep from which he was aroused with difficulty. At this time the attendant may notice various abnormalities of behaviour, the subject showing clumsiness with his apparatus, loss of balanced judgment, fidgeting, or the unnatural disinterest already mentioned. A sensation of depression or constriction, frequently indescribable, in the epigastrium or in the praecordium may be experienced. Visual or auditory hallucinations are late phenomena and mean that the end-point is not far off. They have only occasionally been reported in the earlier crises. Visual disturbances include flashes of light, usually in the centre of the visual fields, haloes round objects, lateral movements of images, micropsia, and apparent changes in illumination. Auditory hallucinations such as bell-ringing and knocking are far less common. Both deafness and hyperacuity are encountered. Elaborate auditory or visual hallucinations, which are classified clinically under psychical seizures, are not experienced. (Unpleasant tastes and odours have not been encountered in the "dry" but were reported by two subjects in the "wet.") Constriction of the visual fields occurs only after prolonged exposures, is gradual in onset, and can be marked, without the more acute manifestations of oxygen poisoning. In a few cases nausea and vertigo, together or separately, become so severe that the subject reverts to air-breathing before convulsive symptoms appear.

Definite twitching of the lips usually means that the end-point is near. This is the most common termination. The twitches are powerful and sustained. They are usually first seen on one side of the upper lip, but if the exposure continues they increase in power and frequency and spread to the whole mouth and face and sometimes to other parts of the body. On occasion a marked twitch is followed by a long period of quiescence before recurrence. This is exceptional, and in most cases, if oxygen-breathing continues, convulsive movements of the lips pass into generalized jactitations or convulsions. Twitching of the cheek and nose are often seen with or without lip-twitching. Occasionally there is isolated twitching of the arm, leg, spinal, or abdominal muscles.

In some cases a few seconds or minutes before the end the respirations, which are normal and serene throughout, show a number of abnormalities. The commonest occurrence is rapid panting. In other instances there is marked inspiratory predominance, reminiscent of asthma, but without wheezing. Respirations sometimes become grunting in character, and in severe cases this may develop into an acute state of apnoea in the inspiratory position. Subjects with severe respiratory symptoms usually convulse, although a few escape on being turned on to air.

It will be seen that an accurate description of such a varying picture is not easy. The clinical impression gained was of two distinct processes occurring in many different patterns. One is an insidious intoxication which may affect the function of practically any part of the central nervous system, and added to this is an increasing convulsant tendency that is usually, but not always, first manifested in the facial muscles and finally becomes generalized. There are great variations in the resistance to the general background of intoxication and in the resistance to the convulsant factor. Certain individuals may show powerful twitching movements, either localized or generalized, but retain consciousness, while others pass into what is indistinguishable from an epileptic fit immediately after such convulsive movements and sometimes in their complete absence.

The syncopal type of attack was seen on only a few occasions. There were usually associated muscular twitchings. One of these subjects appeared like a case of so-called "shock," being pale, flaccid, and in a cold sweat, with a poor pulse. He did not convulse. The blood pressure was not ascertained. Another subject collapsed but did not appear to be "shocked." He was unable to move or speak, although he appreciated his surroundings. Such states are described in epilepsy under the name of cataplexy. Space does not allow the description of individual exposures.

Convulsive Attacks

The convulsive attacks of oxygen poisoning were on the average of two minutes' duration, the subject being unconscious. If the subject was turned on to air immediately the convulsion started only one attack resulted. In one case where oxygen breathing was inadvertently continued a second convulsion began after a pause of about thirty seconds. Incontinence occurred in a number of instances. Detailed description of these attacks is unnecessary as they in no way differed from a major convulsive attack of idiopathic epilepsy.

Confusion, dissociation, headache, nausea, and vomiting as experienced after an epileptic fit occurred in many cases. Some individuals showed marked emotional instability, which is not a feature of leptazol or electrically induced post-convulsive states. The majority, however,

were subdued and ataxic for about 15 minutes after, and if left alone fell asleep. Occasionally subjects complained of pronounced photophobia. In a number of cases there was post-convulsive automatism, the subject suffering from complete amnesia for a period from one-half to seven hours. There were some stiff backs and subcutaneous extravasation due to muscular violence.

Off-effect

A number of subjects suffered marked exacerbation of symptoms after returning to air-breathing. Severe nausea, increasing pallor, sweating, and vertigo have all occurred in subjects who were previously symptomless. Other subjects showed a sudden dissociation and panting. In a few cases it appeared that convulsions were precipitated by reverting to air-breathing. A possible explanation of this off-effect may be the sudden fall in oxygen tension, causing temporary cessation of respiration in already damaged nerve cells. In some cases, no doubt, the toxaemia was already of such a degree that convulsions were inevitable. Decompression appears to precipitate convulsions in such subjects and also in animals. The "startle" phenomenon, where sudden and unusual sensory stimuli precipitate convulsions—that is, decompression—may account for some of these cases.* It has therefore become a rule in this work that if a subject has severe symptoms and reverts to air-breathing he is not decompressed until his symptoms have gone and relative normality has been attained.

The recovery from a non-convulsant end-point is remarkably rapid and the subject appears normal in five minutes or less. All twitching usually disappears in about a minute. The subject may appear dazed for a few minutes longer and his respirations are inclined to be irregular, with intermittent deep excursions. Euphoria is frequent, but this may well be due to relief at having survived a toxic exposure without convulsing. In some cases pallor persists for as long as an hour, and sometimes the subject behaves as if he were slightly drunk for the same period. This latter syndrome is known in experimental diving circles as "oxygen jag."

Oxygen Poisoning under Water

So far only signs and symptoms as seen in the "dry" have been described. In a series of 388 dives to end-point, under water, the following symptoms were recorded: convulsions in 46 (9.2%) cases; twitching of lips, 303 (60.6%); vertigo, 44 (8.8%); nausea, 43 (8.3%); respiratory disturbances, 19 (3.8%); twitching of parts other than lips, 16 (3.2%); sensations of abnormality (drowsiness, numbness, confusion, etc.), 16 (3.2%); visual disturbances, 5 (1%); acoustic hallucinations, 3 (0.6%); paraesthesiae, 2 (0.4%). The most striking observation is the remarkable predominance of lip-twitching. It is probable that many of the more subtle symptoms occurred but that they were difficult to appreciate under water. A number of divers who reported severe lip-twitching, and were hauled up jactitating and confused but did not convulse, remembered only severe lip-twitching as their end-point. Further observations by the attendant at such a critical time were difficult, particularly with the subject in a diving-suit.

Since Bornstein's single experiment in the "dry" (1912) it has often been stated that exercise at toxic tensions caused twitching of the muscles employed. In a series of "wet" dives to toxic depths with hard work symptoms were analysed in 120 end-points. The findings were as follows: Convulsed, 6.8%; lip-twitching, 50%; vertigo, 20.8%; nausea (vomiting two cases), 17.5%; choking sensations, 2.5%; dyspnoea, 2.5%; body tremors, 1.7%.

It appears that nausea and vertigo increase in frequency if the subject is exercising. Twitching of the muscles being exercised was not encountered in the whole series. Carbon dioxide absorption has to be extremely efficient with hard work, especially in air, where the canister becomes very hot, and a large series of such experiments in the "dry" were marred by inadequate carbon dioxide absorption and are not reported here. In these "spoiled" experiments the subjects experienced twitching of muscles and severe tremors, and this was shown to be due to high tensions of carbon dioxide in the circuit.

Subjects breathing oxygen at increased tensions before toxic signs or symptoms occur are remarkably normal. The mental torpidity described by some observers has not been noted, even at considerable depths, except after long exposures in the "dry." Judgment and the capacity for hard physical work appear to be in no way impaired. Under-water divers are more free of symptoms than those in the "dry" right up to the moment of lip-twitching or convulsing. No doubt the abnormal environment and accoutrement obscure the minor premonitory symptoms. This apparent normality and the frequent suddenness of convulsive symptoms make oxygen-breathing under water at toxic depths highly dangerous, particularly as the subject often gains a very false sense of security.

Special Investigations

These experiments were carried out under war conditions, and owing to the urgency of the work and the many other immediate operational problems being investigated it was unfortunately not possible to extract the maximum data from this unique series by elaborate special investigations. However, a number of important observations were made, and these will now be considered under appropriate headings.

"Lorrain Smith Effect" (Pulmonary Damage) in the Human

Lorrain Smith (1899) reported fatal pneumonia in a rat after four days' exposure to 73% oxygen. Many animal experiments have been carried out since, and the general conclusion has been that 60% oxygen causes no pulmonary damage in animals or man (Barach, 1926) even after indefinitely prolonged exposures. Becker-Freyseng and Clamann (1939) produced bronchopneumonia in a healthy man by breathing 90% oxygen for 60 hours.

In over 1,000 experiments where subjects were breathing oxygen at toxic pressure (4.68–1.9 ats. abs.) the exposure was always terminated owing to signs or symptoms involving the central nervous system. Frequent chest examinations were completely negative. At more shallow depths, however, nervous symptoms are encountered only after very long exposures or not at all. It was thought possible that there might be a greater risk of lung damage at such depths. Dives up to three hours at 2.1 ats. abs. in the "wet" caused no pulmonary irritation. A series of prolonged dives to 12 ft. (3.7 m.; 1.36 ats. abs.) with periods at 50 ft. (15.2 m.; 2.5 ats. abs.) gave equally negative results. An example was a dive for 6 hours 9 minutes, continuously in oxygen at 12 ft. (5 hours 39 minutes) and at 50 ft. (30 minutes), where no pulmonary irritation was encountered.

It can be stated with reasonable certainty that no real under-water dive will be made where lung damage will result from high tensions of oxygen, and that at depths greater than 30 ft. (9.2 m.) nervous symptoms will terminate the dive long before any pulmonary irritation occurs. Lorrain Smith (1899) reported that a rat died of pulmonary damage after 20 minutes at 4.5 ats. abs. of oxygen, yet a subject completed 61 minutes at 4.6 ats. abs., breathing oxygen, with no demonstrable pulmonary damage. Total evidence suggests that man has more resistance to lung damage than small experimental animals.

* Since writing this article it has been noted that a similar suggestion was made by J. W. Bean (1945).

A number of these subjects breathed oxygen at increased tensions several times a week for two years. It was considered possible that although the pulmonary damage suffered in a single exposure was inappreciable there might be a cumulative effect. Frequent routine examinations of the subjects' chests were therefore carried out. Radiographs were taken regularly and the vital capacities noted. In not a single case has there been any positive finding suggestive of lung damage. The subject who dived to 70 ft. (21.3 m.) to end-point two or three times a week for three months won the Portsmouth middle-weight boxing championship during this period. It would appear that there is no cumulative effect on the lungs in oxygen-diving.

Cardiovascular Findings

Benedict and Higgins (1911) reported bradycardia in man breathing increased percentages of oxygen at atmospheric pressure. This finding has often been confirmed, both in man and in animals. Bean and Rottschafer (1938) showed with animals that, although the bradycardia was mediated by the vagus, blocking of this nerve had no effect on oxygen poisoning. In the experiments described here it was found that, although the pulse changes were little more than could be accounted for by prolonged basal conditions, there was in some cases a marked slowing of the pulse (35–50), particularly after long exposures at 60 ft. (18.3 m.). The pulse was regular and there was no suggestion of dropped beat or any type of heart-block. Some of these subjects who did not convulse did not recover their normal rate till several hours after the exposure. The degree and rate of onset of the bradycardia had no fixed relation to tolerance or other symptoms, nor did the pulse changes give any warning of acute symptoms or convulsions.

Only a limited number of blood-pressure recordings were made at 90 ft. (27.4 m.). There was a gradual rise of both systolic and diastolic pressures, which stabilized after some 20 minutes at about 15 mm. above the normal levels. Just before the onset of acute symptoms a further brisk rise of about 15–20 mm. occurred. These findings are similar to those of Behnke *et al.* (1935–6). Microscopical study of the subjects' nail-bed capillaries while under toxic tensions and while suffering acute symptoms revealed no significant changes. *X*-ray and clinical examinations have shown no enlargement of the heart in subjects who were often exposed to toxic tensions over a long period. It is difficult to see why this should occur unless there is severe pulmonary damage, but it is a common belief among medical officers and divers, particularly in the Italian Navy, that oxygen-breathing increases the size of the heart. This was not confirmed.

Neurological Findings

In experiments continued over a period of three years no adverse after-effect has been noted in any subject's neurological integrity, intellectual ability, or personality. Neurological examination of subjects while breathing oxygen at 60 ft. (18.2 m.) and 90 ft. (27.4 m.) in the "dry" showed no significant change in reflex activity. Constriction of the visual field has already been mentioned. Some subjects showed marked dilatation of the pupils as they approached the end of the exposure. The only other important finding was the development of a positive Chvostek sign in a number of subjects during exposures. Although this usually developed in the latter half of the exposure, it was not a reliable sign of the approach of acute symptoms, although if present it became more marked as the exposure continued. Some subjects had an acute end-point without the occurrence of a positive Chvostek sign at any time. Controls in air at atmospheric pressure revealed that a few otherwise normal subjects had a positive Chvostek sign, which in some cases was present one day and absent on another. Such a finding in air, or even developing during the exposure, did not necessarily signify poor oxygen tolerance. In one quite unique subject acute symptoms always started with twitching of the muscles of the left hand (the only case of twitching of the hand recorded in the whole series), which then spread up the arm to the shoulder, and on two occasions this was followed by convulsions. This series of events was similar to a Jacksonian attack and quite unlike the usual muscular twitching.

Electro-encephalographical Findings*

Briefly, exposure to oxygen at 120 ft. (36.6 m.) had no immediate effect on the E.E.G. recordings. In general there was a slight increase of fast activity (25–32 p/s) and also increase in voltage of the 3–5 p/s waves. Coupled with this was a progressive decrease of the amount and voltage of the dominant frequencies (6–12 p/s). The tracings tended towards a sequence of 3–5 p/s waves with a superimposed ripple of fast activity. These abnormalities were episodic. Infrequently, spikes—that is, single high-voltage fast sine waves—appeared and increased in number. They were bilateral and symmetrical. Subjects who had non-convulsant end-points showed no other changes. Those who convulsed gave a picture of electrical activity during and after the fit which was indistinguishable from that seen in grand-mal epilepsy. It was apparent that there was nothing specific in the convulsions of oxygen-poisoning, as regards electrical activity, once they had started. In some cases there were signs of disturbance—that is, short bursts of 5 p/s activity with increasing voltage just before the attack. Others showed no change of cortical electrical activity before the major convulsive attack. In view of the similarity of the convulsions, both clinically and electrically, to those of epilepsy it was thought that a study of the E.E.G. of subjects in air, and with hyperventilation, might show inborn instabilities that could be correlated with oxygen tolerance. Fifteen subjects from the Admiralty Experimental Diving Unit were graded in order of average oxygen tolerance. This was based on many dives at various depths in the "wet" and in the "dry" over a long period. There was no statistically significant correlation, although the three most resistant subjects had normal E.E.G.s. However, the other two "normals" occurred in the last five in the endurance rating. No "normals" had convulsed at this time, but two did so in the later experiments.

Electromyographs of the lower facial muscles showed bursts of potential with lip-twitching without any associated abnormality of cortical electrical activity. Conversely, bursts of fast cortical activity occurred without increase in muscle action potential. Observations showed that clonic movements or twitching of peripheral muscles was not necessarily associated with changes in the E.E.G.

Toxic Effects of Oxygen on Brain Metabolism

Prof. F. Dickens (1946), in associated M.R.C. (R.N.P.R.C.) research, investigated the action of high-pressure oxygen on rat-brain slices. This work is briefly referred to here for the sake of completeness. He showed that the respiration of isolated cerebral cortical tissue is progressively and irreversibly poisoned. Curves plotting the percentage fall of initial respiratory rate against time were remarkably similar in type to those showing the elimination of a group of individuals by toxic symptoms at a fixed depth (see Fig. 4 "dry"). The time/pressure relationship for a fixed degree of respiratory poisoning was also of a similar type to that obtained for the means of times causing acute symptoms in a group of men at various depths. The order of sensitivity to high pressures of oxygen of the various rat tissues was as follows: Brain cortex > spinal cord > liver > testes > kidney > lung > muscles. The actual tension of oxygen in the brain tissue *in vivo* and *in vitro* under these conditions is not yet accurately known, but from Dickens's experiments it is certain that convulsions occur in man and animals when the brain tissue respiration is but minutely impaired. A similar problem is presented by the effect of narcotics on brain slices and *in vivo* (Quastel, 1939). Dickens presents strong evidence that the primary effect may be in the inhibition of pyruvic oxidase, and that the secondary effects would be general poisoning of carbohydrate oxidation, since all known paths of carbohydrate oxidation converge at the stage of pyruvate. Magnesium, manganese, and cobalt ions strongly protect pyruvic oxidase from oxygen poisoning in tissue slices. Protection by metallic ions is not entirely similar *in vivo* in animal experiments (Marks, 1944). In view of the known –SH character of this enzyme and the known ability of these metals to protect this group, it is likely that

* These unpublished E.E.G. investigations were carried out in the later collateral M.R.C. (R.N.P.R.C.) research by Brown, Downman, MacIntosh, and Williams. The unit subjects were employed in a number of the experiments.

the -SH group of pyruvic oxidase is the seat of oxygen poisoning. The irreversibility of the poisoning in these experiments may be explained by the known difficulty of reconstituting the -SH group *in vitro*. If, as it appears, convulsions or acute symptoms occur in a very early stage of this process, then reactivation in the more physiological conditions of the intact organism is extremely feasible. This would account for the reversibility of acute oxygen poisoning in man and animals if the exposure is immediately discontinued.

Discussion

The most important aspect of oxygen poisoning is the intoxication of the central nervous system. It seems that the whole cerebrospinal axis is involved. The twitching of the muscles is definitely subcortical in origin, and the sensitivity of the facial nerve to tapping would indicate that even the most peripheral components are affected. Meanwhile the cortex is also being poisoned, and in a number of cases phenomena exactly similar to epileptic auras occur which are presumably due to cortical dysfunction. In some cases severe muscle-twitching, and even convulsions, may be precipitated without any such aura being reported. The more peripheral motor discharges may predominate throughout and even cause generalized jactitations without electrical or clinical evidence of cortical disturbance. In other cases non-convulsant cortical disturbances may cause symptoms of such severity that the exposure is discontinued. The remarkable individual variation in reaction to unphysiological tensions of oxygen is again emphasized.

It is not known why the lips should be so specifically affected. The possibility of the added irritation and fatigue caused by the mouthpiece was considered, but was excluded by the demonstration of lip-twitching in man in helmets without mouthpieces (Donald, 1942), and also in rabbits and other animals (Marks, 1944). These peripheral twitching movements are almost certainly related to the myoclonic seizures of epilepsy, in contrast to the Jacksonian type of attack. These myoclonic seizures commonly affect the face, but can occur elsewhere. Penfield and Erickson (1941) concluded from electro-encephalographic studies that these attacks originate from the grey matter in the brain stem and spinal cord. It is significant that a similar conclusion has been reached with regard to the origin of the muscular twitching in this work. Of equal interest is the comparative rarity of myoclonic seizures and frequency of Jacksonian seizures in epilepsy, and the reverse in oxygen poisoning. The rarity of somato-sensory disturbances (paraesthesiae) and elaborate hallucinations (perhaps associated with absence of petit mal) is worthy of note. At no time was any attack akin to petit mal observed either clinically or electrically. Thus even in oxygen poisoning, in which epileptic auras are closely imitated, petit mal is unknown. This emphasizes the uniqueness and importance of that phenomenon in idiopathic epilepsy.

A small group of naval epileptics (five) tested by the M.R.C. workers did not show any apparent increase of sensitivity to oxygen poisoning, but the experiments were too few for definite conclusions to be drawn. Penfield emphasizes the great variability in the physiological state of the epileptic cortex. "It may be quite normal in reaction, or it may be abnormally stimulable, completely refractory, or at other times unequally hyperactive." Such variability of behaviour combined with the enormous variability of human susceptibility to high pressures of oxygen makes a far larger series of experiments desirable. However, the pattern of toxic symptoms appeared similar to those in normals, and the general impression gained was that there was no essential difference of reaction, or any increased accessibility to the convulsant mechanism, by the channels or processes involved in oxygen poisoning. It is possible, and indeed highly probable, that there are distinct chemical or cellular systems the adequate and separate disturbance of which will allow or cause convulsions. On first principles it would appear likely that the depression of essential carbohydrate oxidation in nerve cells would cause depression in function and not increased activity. If this is the case, then the "auras," motor twitches, and convulsions are more likely to be release phenomena and not due to primary excitability of the parts of the central nervous system concerned. The sudden violent discharge to utter exhaustion (as shown in convulsions by the E.E.G.) is strange behaviour in cells in which the oxidative processes are damaged.

The relatively slow and deliberate evolution of auras akin to those experienced in epilepsy is, so far as I know, unique to oxygen poisoning and should be further exploited by experimental workers. Although the condition is artificially produced, it approximates far more closely to the natural epileptic phenomenon than other induced convulsant states. The electrical localization of epileptic discharges in idiopathic non-convulsant equivalents has already been carried out in a number of cases. It would be possible to select resistant subjects who experienced definite auras without marked "peripheral" motor discharges. The electrical study of these auras in such subjects would be a new approach to the problems of cortical localization and function. Further study of the various patterns of cortical dysrhythmias before convulsions may contribute to the knowledge of the mechanisms of epilepsy.

The therapeutic use of oxygen as a convulsant in the various psychoses has been suggested in the past, but the lack of knowledge of the syndrome, combined with the greater ease and safety of other methods, has so far prevented its use for this purpose. The complicated and rather frightening ritual (to strangers) of pressure work and breathing from a closed circuit, render the value of this method very questionable. Changes in the central nervous system could be induced up to the point of convulsions. With experienced attendants these could be avoided in most cases if desired. Evidence may be obtained as to whether the improvement, if any, was caused by such changes alone or by the convulsions they can precipitate.

Conclusions

In the first large series of experiments on human beings, knowledge of the dangers and symptoms of oxygen poisoning has been expanded. It has been demonstrated that these dangers are far greater than was previously realized. The variation of tolerance between individuals, the variation of tolerance of each individual, the impairment of tolerance with work and under water, all make diving on pure oxygen below 25 ft. (7.6 m.) of sea-water a hazardous gamble. The impairment of tolerance under water is as mysterious as it is unfortunate. Despite the fact that a comprehensive picture of human symptoms of oxygen poisoning is now available, it is emphasized that no signs or symptoms can be given that would ensure a timely cessation of oxygen-breathing in all cases. The variation of symptoms even in the same individual, and at times their complete absence before convulsions, constitute a grave menace to the independent oxygen-diver. The only possible conclusion is that such tensions of oxygen should be scrupulously avoided.

Summary

Previous research into the effect of increased tensions of oxygen on man up to the commencement of this work is briefly described.

An account is given of experiments to determine the tolerance of groups of men to such tensions of oxygen under varying conditions.

The signs and symptoms of oxygen poisoning in man are described.

The possibility of pulmonary damage by increased tensions of oxygen is discussed.

Electrical and chemical changes in the central nervous system are briefly described.

The relation of oxygen poisoning to epilepsy and the possibilities of further useful investigations are discussed.

The danger of breathing oxygen at increased tensions is emphasized.

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SUPEROXIDE DISMUTASES ×877

Irwin Fridovich
Department of Biochemistry, Duke University Medical Center, Durham, North Carolina 27710

CONTENTS

INTRODUCTION

There is a bizarre enzymatic activity universally present in respiring cells. The substrate is an unstable free radical that can be present only in minuscule amounts at any instant, and the reaction catalyzed proceeds at a rapid rate even in the absence of the enzyme. Yet the enzyme is essential for the survival of aerobic cells. It catalytically scavenges the superoxide radical, which appears to be an important agent of the toxicity of oxygen, and thus provides a defense against this aspect of oxygen toxicity. The reaction whose rate it enhances is a disproportionation or dismutation of these radicals and may be written

$$O_2^- + O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$$

This activity was discovered only recently (1, 2) and, given the instability of O_2^-, it is not surprising that this finding was long delayed and finally achieved by following chance observations rather than by design. During the past few years there has been a surge of interest in this enzymatic activity and a voluminous literature has accumulated. This is an intellectually exciting situation but it puts the reviewer in an unenviable position. Thus it is clear that the continued rapid appearance of new reports on this subject will inevitably render this review out of date by the time it reaches its readers. Furthermore, speculations which seemed both bright and reasonable at the time of writing may appear trite or quaint at the time of reading.

Nevertheless, the attempt must be made. Hopefully this review will carry the story a bit further than did its predecessors (3–7).

SUPEROXIDE RADICAL AND THE DISMUTATION REACTIONS

O_2^- is a common intermediate of oxygen reduction. This is a consequence of the fact that molecular oxygen in its ground state prefers univalent pathways of reduction. The electronic basis for this preference rests upon a spin restriction, which has been discussed by Taube (8). In any case, a number of reactions of interest to biochemists have been shown to generate O_2^-. Among these are the autoxidations of hydroquinones, leucoflavins, and catechol amines (9–16), thiols (17), reduced dyes (9, 18, 19), tetrahydropteridines (20), ferredoxins (21–24), rubredoxin (25), and hemoproteins (26–28). Furthermore, the catalytic actions of several enzymes have been shown to evolve O_2^-. This category includes xanthine oxidase (2, 29, 30), aldehyde oxidase (31, 32), dihydro-orotic dehydrogenase (33), and a group of flavoprotein dehydrogenases (14). In addition, there are several oxidases and hydroxylases inhibited by superoxide dismutase, which suggests that O_2^- is an intermediate in their catalytic cycles. These include tryptophan dioxygenase (34), the reconstituted liver microsomal hydroxylase (35), soluble hydroxylases from *Aspergillus niger* (36), and galactose oxidase (37). Finally, O_2^- is produced by intact granulocytes during the act of phagocytosis (38–41), by illuminated chloroplasts (42–46), and by lyophilized rat liver microsomes (47, 48). Thus, although we remain ignorant of the identity of the quantitatively most significant sources of O_2^- within any given type of cell and of the absolute rates of O_2^- production inside cells, we can feel secure in concluding that respiring cells will produce significant amounts of O_2^-.

The superoxide radical cannot accumulate in aqueous media because it readily undergoes a disproportionation or dismutation reaction. O_2^- is the conjugate base of a weak acid called the hydroperoxyl radical whose pK_a is 4.8. The pH dependence of the spontaneous dismutation can be explained on the basis of this pK_a and on the following reactions (49)

$$HO_2^{\cdot} + HO_2^{\cdot} \rightarrow H_2O_2 + O_2 \qquad = 7.6 \times 10^5\ M^{-1}sec^{-1}$$

$$HO_2^{\cdot} + O_2^- + H^+ \rightarrow H_2O_2 + O_2 \qquad = 8.5 \times 10^7\ M^{-1}sec^{-1}$$

$$O_2^- + O_2^- + 2H^+ \rightarrow H_2O_2 + O_2 \qquad < 100\ M^{-1}sec^{-1}$$

At pH 7.4 the rate constant for the spontaneous dismutation reaction is approximately $2 \times 10^5\ M^{-1}sec^{-1}$. Can one hope to significantly accelerate the rate of O_2^- decay at this pH through the action of an enzyme such as superoxide dismutase? An affirmative answer to this question depends upon two factors. The first is that the rate constant for the reaction of O_2^- with superoxide dismutase is close to $2 \times 10^9\ M^{-1}sec^{-1}$. At pH 7.4 this gives the catalyzed reaction an advantage of 10^4 over the spontaneous dismutation. The second point in favor of the enzymatic dismutation is that the concentration of the enzyme inside cells vastly exceeds the steady state concentration of O_2^-. Therefore the collision rate of a superoxide radical with enzyme will be much greater than its rate of collision with another O_2^-. In whole

human liver we estimate the concentration of superoxide dismutase to be at least 3×10^{-5} M; whereas the steady state concentration of O_2^- must be at least five orders of magnitude lower. This gives the enzymatic decay of O_2^- another advantage of at least 10^5. Taken together these two factors would make the enzyme-catalyzed decay of O_2^- at pH 7.4 in liver at least 10^9 times faster than the spontaneous decay.

ASSAYS FOR SUPEROXIDE DISMUTASE ACTIVITY

The first requirement for productive study of an enzyme is a convenient and precise assay. In the case of superoxide dismutase, the instability of its substrate has forced circuitous approaches to this goal. One successful strategy combines a reaction that generates O_2^- with an indicating scavenger for this radical. In such a case, the superoxide dismutase competes with the indicating scavenger for the flux of O_2^- and thus inhibits modification of the scavenger. Xanthine oxidase acting aerobically upon xanthine generates O_2^-, which can be detected by its ability to reduce cytochrome *c*. The reduction of cytochrome *c*, which can be followed at 550 nm, will then be inhibited by superoxide dismutase. One unit of activity can be defined as the amount that causes 50% inhibition of the reduction of cytochrome *c* under specified conditions. In the first isolation of superoxide dismutase, this assay provided a sensitivity such that one unit was 0.1 μg/ml of the enzyme (2). The sensitivity of this assay can be increased greatly by raising the pH and by diminishing the concentration of cytochrome *c*. O_2^- can be introduced into solutions by means other than the xanthine oxidase reaction, and indicating scavengers of O_2^- other than cytochrome *c* can be very useful. Much of this has been reviewed previously (7). Very simple assays for superoxide dismutase can be achieved on the basis of its ability to inhibit free radical chain oxidations in which O_2^- is either an initiator or a chain-propagating radical. Reactions that have been useful in this way include the autoxidations of sulfite (49a), epinephrine (11), and pyrogallol (13).

It is unusual to assay an enzyme on the basis of its ability to inhibit some observable process. A direct assay in which superoxide dismutase accelerated the rate of substrate consumption or product production would certainly be conceptually preferable to the indirect assays described above. Direct assessment of the catalytic action of superoxide dismutase has been achieved by following the disappearance of O_2^- by means of electron paramagnetic resonance (EPR) (15) or by direct ultraviolet spectrophotometry (50, 51). In the latter cases high concentrations of O_2^- were rapidly generated in oxygenated aqueous solutions by pulse radiolysis, such that direct observations of its ultraviolet absorbance were feasible. These and similar studies have been very important in probing the mechanism of action of superoxide dismutases.

BIOLOGICAL IMPORTANCE OF SUPEROXIDE DISMUTASE

There are good reasons for concluding that respiring cells generate O_2^-. If we knew enough about the reactivities of O_2^- we could probably deduce the essentiality

of superoxide dismutase. In fact, the chemistry and biochemistry of O_2^- are still in a primitive state, so it has been necessary to obtain empirical support for the importance of the dismutase. This has been done and there are several lines of evidence indicating that this enzyme is essential for the survival of respiring cells: 1. Only respiring cells can possibly produce O_2^-, hence only they should need a defense against it. Surveys of a variety of microorganisms demonstrated that the aerobic and aerotolerant species contained superoxide dismutase, whereas the obligate anaerobes did not (52). The only aerotolerant species that lacked this enzyme was found unable to utilize oxygen (53). 2. Superoxide dismutase is inducible by oxygen in *Streptococcus faecalis* (54), *Escherichia coli* B (55), and *Saccharomyces cerevisiae* (56). This induction allows manipulation of the intracellular level of the enzyme by variation of the oxygen tension under which the cells are grown. If O_2^- is an important agent of oxygen toxicity and if superoxide dismutase is the defense, then cells with the induced, high levels of the enzyme should thereby be rendered resistant to hyperbaric oxygen. This was shown to be the case (54–56). The strength of this argument is augmented by controls demonstrating that *Bacillus subtilis*, in which oxygen induced catalase but not superoxide dismutase, did not gain resistance towards hyperbaric oxygen from growth under oxygen (55). Yet another control involved *E. coli* K12, which responded to oxygen by increasing its content of catalase and peroxidase but not of superoxide dismutase. Growth under oxygen did not make this strain of *E. coli* resistant towards hyperbaric oxygen (56). 3. Mutants of *E. coli* K12 C-600 with a temperature-sensitive defect in superoxide dismutase exhibited a parallel defect in their tolerance for oxygen. Revertants were found to have regained both oxygen tolerance at the restrictive temperature and the ability to maintain normal intracellular levels of superoxide dismutase at this temperature (4). 4. Streptonigrin, whose lethality towards *E. coli* is augmented by oxygen, has been supposed to act by serving as an intracellular source of O_2^- (57–59). Induction of superoxide dismutase by oxygen might therefore be expected to provide some tolerance towards this antibiotic. This has been observed (55).

The results obtained with microorganisms establish that superoxide dismutase is an essential defense against oxygen and superoxide toxicity. There are data indicating that this is true also of higher organisms. 5. Cultures of fetal calf myoblasts were damaged when exposed to light in the presence of FMN plus EDTA, and superoxide dismutase added to the medium protected these cells against the lethality of this photochemical flux of O_2^- (59a). Anthracene, methylcholanthrene, or benzpyrene, at levels innocuous when applied alone, markedly enhanced the cytotoxic effects of the photochemical flux of radicals, and once again superoxide dismutase protected. Superoxide dismutase was also reported to provide some protection against the deleterious actions of γ irradiation (59a). 6. Rats exposed to 85% oxygen become adapted to it and will then tolerate 100% oxygen, which would prove lethal in the absence of the adaptation. A modest but reproducible increase in lung superoxide dismutase has been shown to parallel adaptation (60). 7. Glutathione induces a swelling of rat liver mitochondria which is prevented by superoxide dismutase (61). 8. Paraquat introduced into rats causes lung damage whatever the route of administration. Since lung is the most aerobic of the tissues, this leads to the speculation

that paraquat, like streptonigrin, may enhance oxygen toxicity by acting as an efficient source of O_2^-. Superoxide dismutase injected at frequent intervals has been reported to diminish the toxicity of paraquat (62).

VARIETIES OF SUPEROXIDE DISMUTASES

A common stress progressively applied to a varied biota is likely to force parallel and independent adaptations among the surviving species. The oxygenation of the earth's atmosphere, due to the photosynthetic activity of blue-green algae, certainly must have constituted such a stress to which superoxide dismutase would be one appropriate adaptation. Since a considerable diversification of life forms must have preceded the appearance of blue-green algae, we need not be surprised to find more than one type of superoxide dismutase among present organisms. There are, in fact, several of these enzymes.

Copper- and Zinc-Containing Superoxide Dismutases

The cytosols of eukaryotic cells contain a superoxide dismutase that has a molecular weight of 32,000, is made up of two identical subunits, and contains one Cu^{2+} and one Zn^{2+} per subunit. The properties of this superoxide dismutase have been remarkably resistant to evolutionary modification, and the enzymes obtained from fungi, plants, birds, and mammals (45, 63, 68, 69, 71, 72) are hardly distinguishable except by relatively minor differences in amino acid composition and in the super-hyperfine details of the electron spin resonance (ESR) spectra (72). This superoxide dismutase has been reversibly resolved. Activity is partially restored by replacement of Cu^{2+} alone and is fully restored by replacement of both metals (72). Attempts to substitute other metals for the Cu^{2+} have been uniformly unsuccessful, however the Zn^{2+} may be replaced by Co^{2+}, Hg^{2+}, or Cd^{2+} (72–75) without loss of activity.

Structural analysis of the superoxide dismutase from bovine erythrocytes is now in a very satisfactory state. The complete amino acid sequence is known (76–78) and the X-ray diffraction analysis has progressed to a resolution of 3.0 Å (79). It is thus possible to make models of the structure which specify the positions of each amino acid residue and of the Cu^{2+} and Zn^{2+}. This has been done. The most prominent structural feature of this enzyme is a cylinder whose walls are composed of eight strands of the sequence in an antiparallel β structure. The segments of the sequence involved in this β barrel are residues 2–11, 13–23, 26–35, 38–47, 80–88, 91–100, 112–118, and 142–149. The metals are in close proximity. Indeed, the Cu^{2+} and Zn^{2+} are joined by a common ligand; the imidazole ring of His 61. The Cu^{2+} is relatively exposed to solvent whereas the Zn^{2+} is more nearly buried inside the structure. Aside from the shared His 61, the other groups liganded to Cu^{2+} are His 44, 46, and 118, while the other groups liganded to Zn^{2+} are His 78 and 69 and Asp 81 (79). Detailed knowledge of the superoxide dismutase structure will now facilitate further studies of its mechanism. It is impressive that the proximity of the Cu^{2+} and the Zn^{2+} was predicted (73, 80, 81), as was a ligand field for Cu^{2+} composed of histidines (80, 82–84). The mechanism of this enzyme has been probed primarily by means of pulse radiolysis (50, 51, 85–88), and there

is general agreement that the Cu^{2+} is alternately reduced and reoxidized during successive encounters with O_2^-. If direct electron transfer is to occur between O_2^- and Cu^{2+} then the Cu^{2+} must be accessible to water. The structure deduced from sequence and X-ray diffraction analysis indicates that this is the case (79). Results obtained with NMR also indicate that this Cu^{2+} is exposed to solvent (89, 90). Cyanide binds to this Cu^{2+}, and it is the carbon of cyanide which is then immediately liganded to the metal (91). Cyanide is a reversible inhibitor of the Cu^{2+}- and Zn^{2+}-containing superoxide dismutases (50). The oxidation-reduction properties of the Cu^{2+} of superoxide dismutase have been probed. H_2O_2 can reduce this Cu^{2+} but can also irreversibly inactivate the enzyme (92–95) if present at concentrations exceeding 10 μM. The redox interaction between H_2O_2 and the Cu^{2+} must be univalent since the reversal of the superoxide dismutase reaction has been demonstrated (96).

Manganese-Containing Superoxide Dismutases

E. coli B (97) and *Streptococcus mutans* (98) contain a superoxide dismutase which, except for its catalytic activity, appears totally unrelated to the Cu^{2+}- and Zn^{2+}-containing enzyme from eukaryotic cytosols. Thus this bacterial enzyme contains one atom of manganese per subunit, has a molecular weight of 40,000, and is a dimer made up of two subunits of equal size. A manganese-containing superoxide dismutase has been isolated from the luminous mushroom *Pleurotus olearius* and is composed of subunits which, although of identical size, were separable by ion exchange chromatography in the presence of 7.0 M urea (98a). The color and the NMR properties of the *E. coli* enzyme indicate that the manganese it contains is trivalent (99). It appears likely that the mechanism of this bacterial superoxide dismutase will prove similar to that of the Cu^{2+}- and Zn^{2+}-containing enzyme in that it probably depends upon alternate reduction and reoxidation of the active metal. The catalytic activity of the mangani-superoxide dismutase, as a function of pH, has been investigated using the method of kinetic competition (100). At pH 7.0 it is as active as the Cu^{2+}-Zn^{2+} enzyme, but as the pH is raised it becomes progressively less active, whereas the Cu^{2+}-Zn^{2+} enzyme is unaffected by pH in the range 5.5–10.0.

Mitochondria contain a superoxide dismutase strikingly similar to the mangani-enzyme of prokaryotes, with the notable difference that the mitochondrial enzyme contains four subunits instead of two and consequently has a molecular weight of close to 80,000 (71, 101). The similarities in gross properties between the mangani-superoxide dismutases from *E. coli* and chicken liver mitochondria suggested that their relationship might be very close. Partial amino acid sequences have, in fact, been obtained, and they demonstrate that the mitochondrial and the bacterial superoxide dismutases are closely related whereas the mitochondrial and the cytosol enzymes are unrelated (102). This result constitutes powerful support for the theory that mitochondria developed from a prokaryote that entered into an endocellular symbiosis with a protoeukaryote (103). The mangani-superoxide dismutase has recently been isolated from human liver mitochondria and has been found to be very similar to the corresponding enzyme from chicken liver mitochondria (104).

The superoxide dismutase of high molecular weight reported from bovine liver (105) and the isoenzyme B found in a variety of human tissues (106) are undoubtedly the mitochondrial mangani-superoxide dismutase described above. It seems likely that the mangani-superoxide dismutase isolated from *Pleurotus olearius* (98a) will ultimately be found localized in the mitochondria of this eukaryote, since it shares so many properties with the other mitochondrial superoxide dismutases thus far described.

Iron-Containing Superoxide Dismutases

E. coli B actually contains two superoxide dismutases. One of these is the mangani enzyme already discussed while the other is a ferri enzyme localized in the periplasmic space which can be selectively removed from these cells by osmotic shock (107). The gross properties of this enzyme (100, 107) and its amino acid sequence (102) indicate a close relationship to the mangani enzyme from the matrix of *E. coli* and from chicken liver mitochondria. The increase in the superoxide dismutase content of *E. coli* in response to oxygenation is actually due to an increase in the mangani enzyme. Since this was correlated with increased tolerance for hyperbaric oxygen (55), we may conclude that the matrix enzyme serves to scavenge endogenous O_2^-. The levels of the periplasmic ferri enzyme could be modified by nutritional means, and this permitted the demonstration that its role appears to be that of providing a defense against exogenous O_2^- (108). O_2^- has recently been implicated as one of the agents responsible for the bactericidal action of polymorphonuclear leukocytes (38–41). In agreement with this suggestion, *E. coli* B whose periplasmic superoxide dismutase had been elevated by growth in iron-rich media were more resistant towards phagocytic kill than were comparable cells whose ferri-superoxide dismutase levels had been depressed by growth in iron-deficient media (109).

The valence of the iron in this superoxide dismutase has been established as being Fe(III) by EPR (107) and by NMR (99). Very similar enzymes have been found in two species of blue-green algae, *Plectonema boryanum* (110) and *Spirulina platensis* (70), and also in two species of marine bacteria, *Photobacterium sepia* (111) and *Photobacterium leiognathi* (111).

POLEMICS

Every rapidly expanding area of investigation generates polemics. These are usually based upon unrecognized differences in experimental conditions. It is both a beauty and a strength of the scientific method that such disagreements can ultimately be completely resolved by careful experiments, often performed by third parties. A newcomer to the field or a casual reader is likely to be confused by such conflicts while they are yet in progress. To the extent possible, a review should therefore identify and clarify these current polemics.

The subunits of the bovine erythrocyte superoxide dismutase were reported to be covalently linked (112). This conclusion was based upon the observation that the subunits did not dissociate in sodium dodecylsulfate (SDS) unless mercaptoethanol was present. It was subsequently found, however, that this enzyme does not dis-

sociate in SDS, not because its subunits are disulfide bridged, but rather because it is so stable that it is not unfolded by SDS. Indeed, it remains fully active in 1% SDS. It could however be dissociated by heating in SDS or by treatment with SDS plus urea. Mercaptoethanol facilitates dissociation in SDS because an intrachain disulfide bridge contributes to the stability of the holoenzyme (67, 76).

It has been reported that the true biological function of superoxide dismutase is that of scavenging singlet oxygen (113–117). Indeed, it has been suggested that the acronym SOD, used for superoxide dismutase, should stand for singlet oxygen decontaminase (118). This proposal is based upon several instances of the ability of superoxide dismutase to inhibit chemiluminescences, which supposedly originated from singlet oxygen. It is, in fact, difficult to identify the source of a weak chemiluminescence, so it is not safe to equate chemiluminescence with singlet oxygen. Moreover, these measurements were made with photometers capable of responding only in the visible range, whereas singlet oxygen ($^1\Delta g$) should emit in the near infrared. To explain this, the possibility has been entertained that dimers of singlet oxygen form and then emit a single photon in the visible which combines the excitation energy of both members of the pair. There is, however, no evidence for oxygen dimers, either in the ground state or in the excited state (119). Furthermore, singlet oxygen is rapidly quenched by hydroxylic solvents. In water its lifetime is 1×10^{-6} sec (120). Given this short lifetime and the low concentration of superoxide dismutase, which is effective in inhibiting the reported chemiluminescence, one can calculate that the enzyme would have to quench singlet oxygen ($^1\Delta g$) at a rate at least five orders of magnitude greater than that set by the diffusion limit (121). Reports of quenching singlet oxygen by superoxide dismutase may therefore be questioned on theoretical grounds. There is, in addition, direct evidence that superoxide dismutase does not quench singlet oxygen (83, 122–123a). The report that supposedly definitely demonstrated the enzymatic quenching of singlet oxygen by superoxide dismutase (117) was actually flawed in several respects. Thus, it depended upon the decomposition of potassium peroxochromate (V) in water as an exclusive source of singlet oxygen, whereas this decomposition also liberates O_2^- (122). Furthermore, it measured the chemiluminescence of luminol, which in buffered aqueous solutions is always dependent upon O_2^- whatever the oxidant and is therefore always inhibited by superoxide dismutase (124). We may conclude that superoxide dismutase does not act to catalytically scavenge singlet oxygen. Whether or not singlet oxygen is generated within biological systems is an entirely different question and is at present not settled one way or the other.

The copper- and zinc-containing superoxide dismutases found in the cytosols of such diverse eukaryotes as *Neurospora crassa* (63), *Saccharomyces cerevisiae* (65), spinach (69), cow (2), and man (87) are at once remarkably similar to each other and totally different from the superoxide dismutases containing iron or manganese in prokaryotes (70, 97, 98, 100, 107, 110, 111) or in mitochondria (71, 101). Although these similarities and differences can be noted even at the level of gross composition and properties, they have been made dramatically plain by comparison of amino acid sequences (102) which show that the bacterial and the mitochondrial enzymes are closely related to each other, while being unrelated to the enzyme found in

eukaryotic cytosols. These results have clear evolutionary implications which have been discussed (102, 103). It has, however, recently been reported that *Photobacterium leiognathi* contains a superoxide dismutase whose metal components are copper and zinc (124a), and it has been concluded that this argues against the independent evolutionary development of the prokaryotic and the eukaryotic enzymes. This is certainly a fascinating finding but the conclusion it has prompted may be premature. The diagnostic difference between the eukaryotic and prokaryotic types of superoxide dismutase lies in their amino acid sequences, not in the nature of their prosthetic metals. It is entirely possible that the copper- and zinc-containing enzyme reported from *P. leiognathi* could prove to be related to the iron- or manganese-containing enzymes heretofore isolated from prokaryotes or from mitochondria, rather than to the copper- and zinc-containing enzyme heretofore isolated from the cytosols of eukaryotes. This will not be resolved until the sequence data are available.

There have been controversies concerning other aspects of the superoxide dismutase field, such as the presence or absence of tryptophan in the bovine erythrocyte enzyme, the intracellular distribution of superoxide dismutase activity in liver cells, the relative roles of the metal prosthetic groups in the Cu^{2+}- and Zn^{2+}-containing enzyme, and the valence of the manganese in the *E. coli* matrix enzyme. All of these have, in their time, added spice to the pleasures of active research in this area, and all have been resolved by the self-purifying properties of the cooperative-competitive scientific endeavor. These topics have been discussed in this and previous reviews and there is no need to further elaborate upon them here.

SUMMARY AND SPECULATIONS

O_2^- is readily generated by so many spontaneous and enzymatic oxidations that we may assume its production within all respiring organisms. Furthermore superoxide dismutases, which catalytically scavenge O_2^-, are so widespread among respiring organisms that we may assume that O_2^- is a deleterious species whose cytotoxicity has called forth the evolution of defenses, among which are certainly the superoxide dismutases. All of this is supported by the induction of superoxide dismutases by oxygen, by the ability of elevated levels of superoxide dismutase to provide resistance towards the lethality of hyperbaric oxygen and towards the oxygen-dependent lethality of streptonigrin, and finally by the temperature-dependent oxygen sensitivity of temperature-dependent superoxide dismutase mutants. None of this, however, tells us why O_2^- should be cytotoxic. There is the general feeling, based more upon chemical intuition than upon hard facts, that this oxygen-free radical should be reactive towards cellular components; but there is only a little data. Thus O_2^- can certainly act as an oxidant. It causes the oxidation of epinephrine (2), catechols (125, 126), and dehydrogenase-bound NADH (127), and it acts as a chain-carrying species in the autoxidation of epinephrine (11) and pyrogallol (13). O_2^- can also act as a reductant. Its reduction of cytochrome *c* (15, 128) was the basis of the assay for superoxide dismutase activity (2). It also readily reduces the Fe(III) in ferritin (129).

There are other indications of the reactivities of O_2^- in more complex systems. Thus, glutathione causes the swelling of mitochondria, and superoxide dismutase prevents this effect (61). Irradiation of membranes with X rays causes lipid peroxidation, and once again superoxide dismutase protects (130). Isolated inner membranes of mitochondria were peroxidized when incubated with aerobic solutions of glutathione, and superoxide dismutase prevented this lipid peroxidation (116). There have been other reports of the prevention of lipid peroxidation by superoxide dismutase (131, 132). Dialuric acid, which autoxidizes with the production of O_2^-, caused the hemolysis of vitamin E-deficient rat erythrocytes, and superoxide dismutase protected against this cell disruption (133). Bacteria exposed to fluxes of O_2^- were killed, and again superoxide dismutase provided protection (108, 134). Are we to conclude that O_2^- can itself attack the lipid components of membranes?

There is another possibility which seems reasonable and must be further explored. Any reaction generating O_2^- will, by virtue of the spontaneous dismutase reaction, also be generating H_2O_2. Haber & Weiss (135), in studies of the catalytic decomposition of H_2O_2 by iron salts, proposed that O_2^- and H_2O_2 could react as follows: $O_2^- + H_2O_2 \rightarrow OH^- + OH\cdot + O_2$. Since the hydroxyl radical ($OH\cdot$) is an extraordinarily powerful oxidant, this reaction, if it really occurs in dilute aqueous solutions, could vastly amplify the potential dangers of O_2^-. There are indications that the Haber & Weiss reaction is a reality. Thus the action of xanthine oxidase on xanthine liberated ethylene from methional and both O_2^- and H_2O_2 were necessary for ethylene production (136). Furthermore, compounds that scavenge $OH\cdot$ but not O_2^-, such as ethanol or benzoate, prevented this ethylene production. The hydroxyl radical was also detected in this reaction mixture as an oxidant of ferrocytochrome *c* which could be intercepted by ethanol, and the depletion of H_2O_2 by O_2^- was demonstrated as an increased recovery of H_2O_2 in the presence of superoxide dismutase (136). Since then, other instances of the apparent production of $OH\cdot$ from O_2^- and H_2O_2 have been reported (137–140). It seems possible that many of the previously reported effects of O_2^- are in reality effects of $OH\cdot$, generated from the O_2^- by the Haber & Weiss reaction.

It is a sobering thought that the hydroxyl radical, earlier thought of only in connection with the effects of ionizing radiation, may in fact be produced in respiring biological systems. This generates renewed appreciation for the superoxide dismutases, catalases, and peroxidases which, by their combined actions, keep the steady-state concentrations of O_2^- and H_2O_2 vanishingly small and thus minimize the Haber & Weiss reaction and make aerobic life possible.

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Oxygen Poisoning and X-irradiation: A Mechanism in Common[1]

Rebeca Gerschman, Daniel L. Gilbert, Sylvanus W. Nye, Peter Dwyer, and Wallace O. Fenn[2]

Department of Physiology and Vital Economics, The University of Rochester School of Medicine and Dentistry, Rochester, New York

A CONSIDERATION of various isolated reports in the literature has led us to the hypothesis that oxygen poisoning and radiation injury have at least one common basis of action, possibly through the formation of oxidizing free radicals. This article reviews the pertinent material that led to this hypothesis and also presents the supporting evidence obtained from (i) experiments on the protective action against oxygen poisoning by substances of varied chemical nature known to increase resistance to irradiation, and (ii) experiments on the survival in oxygen of mice irradiated and exposed to high oxygen tensions simultaneously or at different intervals.

Concerning free-radical formation, it is generally believed that the chemical actions of ionizing radiation on aqueous solutions are mainly indirect (*1*), involving the primary formation of the free radicals H$^{\bullet}$ and OH$^{\bullet}$ with subsequent formation of H_2O_2, atomic oxygen, and $HO_2^{\bullet}$ (*2*). In the presence of oxygen, increased amounts of the powerful and quantitatively important OH$^{\bullet}$, as well as the less reactive but more persistent $HO_2^{\bullet}$, would be expected.

Free-radical formation is also expected in normal oxidative metabolism. One mechanism by which molecular oxygen can be reduced is the compulsory univalent transfer of electrons described by Michaelis (*3*), according to which, in the presence of protons, one may expect the formation of OH$^{\bullet}$, $HO_2^{\bullet}$, and H_2O_2. Daniels, *et al.* (*4*) have discussed the possible occurrence of an oxidizing free radical $RO_2^{\bullet}$ during the reduction of oxygen, and several other authors (*5–10*) have indicated the occurrence of free radicals as such or bound with enzymes in normal metabolic reactions. As one of the reactants, it might be expected that increased concentrations of oxygen would increase the formation of oxidizing free radicals.

Indication of certain similarities between oxygen poisoning and x-irradiation results from the study of the many reports in the literature dealing with their effects. On the basis that increased metabolism might result in an increased production of free radicals, and vice versa, it is not surprising that variations in oxygen toxicity with metabolic activity have been noted. Thus, in oxygen poisoning, it has been observed that a decreased metabolism has a protective effect and an increased metabolism has a detrimental effect (*11, 12*). Several reports indicate that the same may be true for x-irradiation, but this matter has not been conclusively clarified (*13–15*).

The *in vitro* inactivation of some thiol enzymes has been demonstrated in oxygen poisoning (*16, 17*), and in irradiation (*6, 18*). On the other hand, a measurable *in vivo* decrease of SH groups right after irradiation (*14*) has not been observed. However, one must not necessarily rule out the possibility that the inactivation of SH groups may be responsible in part for the toxic effect of x-irradiation. Thus, Forssberg (*19*) has postulated that, even though a vital component in the cell may be almost completely protected against x-irradiation, the cell may still be highly sensitive in small but vital areas. This same type of reasoning could be applied to oxygen poisoning. Paul Bert and others (*12, 20*) have found that oxygen poisoning causes a decrease in metabolism. Some investigators, on the other hand, have not observed *in vivo* a decreased respiration after oxygen poisoning (*21*) or after x-irradiation (*22, 23*). However, it should be taken into consideration that oxygen uptake may not always be a reliable index of the energy that can be utilized by the cell. For example, if the phosphorylating mechanisms are altered (*24*), then, even though the oxygen uptake may not change or may even increase, the production of utilizable energy may be greatly decreased.

In ionizing radiation, there is evidence that the oxidizing free radicals may be responsible for denaturation of enzymes (*18*) as well as for the depolymerization and other chemical effects on nucleic acids with an associated *in vivo* (*25*) and *in vitro* aftereffect (*4, 26–29*). An *in vitro* aftereffect has also been reported for other substances (*30, 31*).

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TABLE 1. The effect of protective agents* in mice submitted to 6 atm of oxygen.

	No. of animals	Mean survival time (min)	Difference (min)	"P" (%)
Glutathione (67 mg)	20	95.7 ± 6.01	52.9 ± 6.18	0.0
Saline control	20	42.8 ± 1.44		
β-mercaptoethylamine (3 mg)	19	76.9 ± 2.72	31.9 ± 3.53	0.0
Saline control	19	45.0 ± 1.39		
25% ethanol (0.7 ml)	14	59.6 ± 2.18	25.8 ± 3.01	0.0
Saline control	14	33.8 ± 2.07		
Propyl gallate (1.7 mg)†	20	86.7 ± 11.2	44.9 ± 11.4	0.1
Saline control	20	41.8 ± 1.64		
Nordihydroguiaretic acid (2.5 mg)	20	56.1 ± 2.69	13.7 ± 3.17	0.0
Saline control	20	42.4 ± 1.69		
Cysteine (20 mg)	25	59.5 ± 2.80	16.0 ± 3.25	0.0
5% saline control	24	43.5 ± 1.65		
Oxytyramine (5 to 7 mg)	25	48.4 ± 2.71	8.5 ± 3.19	0.8
Saline control	25	39.9 ± 1.68		

* Doses are given per 20-g mouse I.P. Controls included solvents where necessary.
† Propyl gallate in a system containing citric acid and butylated hydroxyanisol.

It has been demonstrated, not only that anoxia decreases the acute lethal effects of ionizing radiations on rats and mice (*32, 33*) and on several other biological systems, but also that increased oxygen tensions enhance the effect of irradiation (*34, 35*). Both oxygen and x-rays produce identical aberrations of chromosomes of *Tradescantia* microspores (*36*) and strikingly similar histological changes in the testis of rats (*37*). Vitamin E (*38–40*), vitamin P (*38, 41*), and cobalt (*16, 42, 43*) have been shown to give some protection against oxygen poisoning and also against x-rays. Insulin, on the other hand, enhances sensitivity to irradiation (*44*) and to oxygen poisoning (*45, 46*).

By virtue of these considerations, we were led to two types of experiments: (i) to test, in the case of oxygen poisoning, the effectiveness of substances that have been demonstrated to protect against x-irradiation; and (ii) to test the combined effect of x-irradiation and oxygen poisoning on the survival of mice.

β-mercaptoethylamine (*47*), ethanol (*48*), glutathione (*49, 50*), cysteine (*51, 52*), and oxytyramine (*53*) have been shown to protect mice against the lethal effect of x-irradiation. Table 1 demonstrates that these agents also increase the survival time of mice exposed to high oxygen tensions. β-mercaptoethylamine is not only of interest because it possesses an SH group, which might account for its protective action, but also because it is part of Coenzyme A. In this connection, Baeq and Herve (*54*) have found that Coenzyme A, in equimolecular concentrations, seems to be much more active than β-mercaptoethylamine as a protector against x-rays. In some preliminary experiments, we have also used Coenzyme A and have found that 3 mg of Pabst Coenzyme A per 20-g mouse, injected intraperitoneally, has some protective action against oxygen poisoning. Since Coenzyme A is a coenzyme for a number of enzymatic systems other than the pyruvic oxidase system, it would be well to keep in mind the possibility that x-rays and high oxygen pressure might affect any of these systems through a primary action on Coenzyme A.

The possible role of changes produced in the oxida-

TABLE 2. Effect of previous radiation on survival of mice in high oxygen pressures with varying intervals between radiation and oxygen exposure.*

Series	Interval	No. of expts.	Pressure (atm)	Sex	Mean survival time (min)			Std. error of dif.†	"P" (%)
					O_2	rad. + O_2	Dif.		
I	Simult.	3	5	m	71.3	56.9	14.4	5.3	0.7
Ia	5 hr	2	5	m	65.0	59.0	6.0	6.4	34.8
II	2 min	2	6	f	49.1	33.9	15.2	2.8	0.0
III	30 min	3	6	f	44.5	39.1	5.4	2.3	1.9
IV	2 hr	4	6	f	35.9	31.4	4.5	1.9	1.8
V	5 hr	3	6	f	35.9	37.2	− 1.3	2.3	56.9
VI	18 hr	3	6	f	40.9	42.8	− 1.9	2.3	40.7

* In each experiment, 20 mice were used, 10 irradiated and 10 controls (occasionally an observation on one mouse was missed).
† Notes on the statistical analysis of the data: There was no evidence of heterogeneity of variance from one group of animals to another of the same sex. Males varied substantially more than females. Within any series of experiments, there was no evidence of interaction between experiments and treatments. The standard errors for each sex are based on a pooled estimate of the within-group variance from all experiments with animals of that sex.

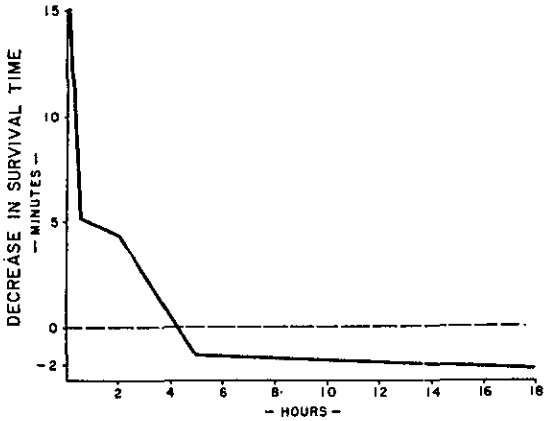

FIG. 1. The ordinates are differences in survival time (min) resulting from exposure to x-irradiation compared with that from exposure to oxygen alone. The abscissas are the intervals between exposure to radiation and to oxygen. The shortest interval is 2 min. The animals remained in the high oxygen until death, and the survival times were measured from the time 6 atm was attained until the time of death. The maximal shortening caused by prior irradiation is 31.0 percent. Data of series II–VI in Table 2.

tion of essential fatty acids by x-rays has been discussed by Mead (*55*) and by oxygen poisoning by Penrod (*56*). Of interest in connection with a preferential oxidation of the "antioxidants" propyl gallate and nordihydroguiaretic acid, demonstrated by Tappel, *et al.* (*57*), is their protective effect against oxygen poisoning, as shown in Table 1. We have also obtained some evidence suggesting a possible protective effect against x-irradiation injury.

In the second type of study, mice were treated with x-rays and oxygen at the same time and in sequence with various intervening periods. In these experiments, the total time of irradiation was about 35 min, and the dose was approximately 8800 roentgens (r) (*58*). The survival times with irradiation in oxygen are given in Table 2. In series I, radiation was applied while the mice were in oxygen (*59*). In series II, oxygen was applied 2 min after the end of radiation and was continued until death occurred. In series III, IV, V, Ia, and VI, a delay of 30 min, 2 hr, 5 hr, 5 hr, and 18 hr, respectively, intervened between the end of radiation and the application of oxygen. Because the experiments with simultaneous irradiation and oxygen poisoning (series I) were done with male mice exposed to 5 atm, and the experiments with varying intervals between irradiation and oxygen poisoning were done with female mice exposed to 6 atm, series Ia was designed to facilitate comparison between these two sets of experiments. When male mice were exposed to 5 atm of oxygen 5 hr after the standard radiation exposure, no significant differences in survival time were noted between irradiated and control mice.

Figure 1 illustrates that irradiation produces an effect that is synergistic with oxygen poisoning in decreasing the survival time of mice exposed to high oxygen pressure. When x-radiation and oxygen are applied simultaneously or within 2 min of each other, a marked decrease of survival time in oxygen is noted. The effect is still significant, although smaller, when oxygen treatment followed radiation by 30 min and 2 hr, and is completely absent or slightly negative after an intervening period of 5 hr.

From the experiments reported and the considerations presented, it would appear that irradiation and oxygen poisoning produce some of their lethal effects through at least one common mechanism, possibly that of the formation of oxidizing free radicals.

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58. The average survival time following this radiation alone was 4.1 ± 0.11 days in 22 mice.
59. One experiment was also tried in which 10 female mice were exposed simultaneously to radiation and oxygen, with another 10 mice exposed to oxygen only. Unfortunately, these mice could not be observed during the radiation because of danger to the observer; and when observations were resumed, 8 of the experimental and 7 of the control mice were already dead. Since no average survival time could be stated, these results are not listed in the table. Female mice are significantly less sensitive to oxygen than males. At a pressure of 5 atm, the female survival times were so widely dispersed that experimentation was difficult. For this reason, simultaneous exposures to radiation and oxygen could be tried only in males.

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Cellular Mechanisms of Oxygen Toxicity[1]

NIELS HAUGAARD

Department of Pharmacology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

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CONCLUDING REMARKS

The investigations reviewed in this article illustrate the variety of the toxic effects of oxygen seen in living organisms exposed to concentrations of oxygen greater than those to which they are adapted. Clearly, oxygen is a substance universally toxic to living cells. It is only by developing special defense mechanisms that animals and plants can survive the ever-present oxidizing potential of the oxygen in their surroundings.

Cells vary greatly in their resistance to poisoning from oxygen, from the vulnerability of the obligatory anaerobic bacterium to the high resistance of the cells of the swim bladder of deep-sea fish. Within each organism, there are differences among tissues in their susceptibility to the toxic effects of oxygen, but the oxygen supply to and the rate of oxygen consumption of a given tissue are important factors in determining the oxygen tension and resulting toxicity.

At present the mechanism of oxygen poisoning and the nature of cellular resistance to the toxic action of oxygen are not well understood. However, the evidence from in vivo and in vitro experiments has become very strong that increased tensions of oxygen produce alterations of cellular metabolism. The metabolic changes eventually lead to disturbance of cell function sufficiently great to produce the symptoms of oxygen poisoning seen in the intact organism.

Numerous enzymes have been found to be capable of inactivation by oxygen and one can consider molecular oxygen to be a potent enzyme inhibitor. Many important nonprotein constituents of the cell can also be oxidized to inactive forms by oxygen. Some of the toxic effects of oxygen observed in vitro may have no relation to the phenomenon of oxygen poisoning in the intact animal and others may play a vital role. Among the effects of OHP that, in the opinion of this reviewer, should be seriously considered as of possible importance in vivo are the following: *1*) oxidation of sulfhydryl-containing coenzymes such as lipoic acid and coenzyme A; *2*) inactivation of enzymes with sulfhydryl groups essential for their activity; *3*) inhibition of iron- and SH-containing flavoproteins; *4*) damage to

cellular membranes by lipid peroxidation; *5*) oxidation of glutathione, ascorbic acid, and possibly other oxidizable tissue components.

Since so many metabolic systems have been shown to be influenced by oxygen at elevated pressures, it is unlikely that oxygen poisoning can be explained on the basis of one primary toxic action of oxygen. It is much more reasonable to suppose that many metabolic alterations occur in cells of a tissue during hyperbaric oxygenation. Depending on the tissue involved and the tension of oxygen, one or another of the metabolic derangements may be of importance in producing the disturbance of cellular function.

The molecular mechanisms involved in the oxidation of labile tissue constituents by oxygen have yet to be understood. Oxygen at increased pressure may increase the rate of oxidation of oxidizable substances by a simple mass action effect. However, the observations that metal ions influence oxygen toxicity profoundly, and the demonstration of a similarity between the effects of OHP and excess radiation, favor the view that free radicals are intermediates at least in some of the toxic effects of oxygen. The studies of peroxidation in various biological systems and the demonstration of a protective effect of antioxidants also provide support for such a concept. Direct measurements of free radical formation during hyperbaric oxygenation is still needed and experimentation in this field is of great importance.

Whatever the detailed mechanisms of the toxic effects of oxygen, there is little doubt that in the intact animal intracellular metabolic changes occur during hyperbaric oxygenation before any signs of toxicity appear. Knowledge of such changes is of the utmost importance for an eventual understanding of the mechanism of oxygen toxicity. The demonstration that the pyridine nucleotides in various tissues become oxidized on exposure of the intact animal to an elevated pressure of oxygen indicates that fundamental reactions involved in glycolysis or energy transfer are inhibited by oxygen. Further studies of early changes in cell metabolism during exposure of whole animals, isolated organs, or cell dispersions to increased pressures of oxygen may well reveal the existence of numerous metabolic alterations that may be of importance in producing the eventual toxic manifestations. Such investigations may also lead to information about metabolic control mechanisms operating in animals at sea level when the tissue oxygen tension varies. It should be emphasized that large changes in cell metabolism and function may occur even if the activity of a rate-limiting enzyme is inhibited only to a small extent, i.e., derangement of cellular activity during hyperbaric oxygenation does not necessarily involve a complete inhibition of a particular metabolic reaction.

The period of delay that exists at all tensions of oxygen before symptoms of toxicity appear indicates that oxidation-reduction buffering systems are present in the cell, analogous to the buffers that maintain cellular pH within a small range. If this is so, glutathione is an important substance to consider for a role in keeping the oxidation-reduction potential constant. It is oxidized by molecular oxygen in the presence of metal ions, but the oxidized form can be rapidly reduced by enzymes in the cell.

In addition to furnishing basic physiological information about the effect of

hyperbaric oxygenation on life processes, future studies of the action of oxygen at elevated pressure on animals and man will be of considerable practical importance. Oxygen toxicity is a real danger under all conditions in which man is exposed to concentrations of oxygen greater than that present in air. This is particularly true for the conditions of hyperbaric oxygenation now used in medicine. A much better understanding of the mechanism of oxygen toxicity than we have now is needed for the safe clinical application of hyperbaric oxygen.

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DEVELOPMENT OF FINE STRUCTURAL DAMAGE TO ALVEOLAR AND CAPILLARY LINING CELLS IN OXYGEN-POISONED RAT LUNGS

GONZAGUE S. KISTLER, PETER R. B. CALDWELL, and EWALD R. WEIBEL

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DEVELOPMENT OF FINE STRUCTURAL DAMAGE TO ALVEOLAR AND CAPILLARY LINING CELLS IN OXYGEN-POISONED RAT LUNGS

GONZAGUE S. KISTLER, PETER R. B. CALDWELL, and EWALD R. WEIBEL

From the Department of Anatomy, University of Zurich, Switzerland, and the 6570th Aerospace Medical Research Laboratories, Wright-Patterson Air Force Base, Ohio. Dr. Caldwell's present address is the Cardiopulmonary Laboratory, First Medical Division, Bellevue Hospital, New York. Dr. Weibel's present address is the Department of Anatomy, University of Berne, Switzerland

ABSTRACT

Rats were exposed to 98.5% oxygen at 765 torr for 6–72 hr. The pulmonary changes were investigated by electron microscopy and by morphometric methods. A progressive thickening of the air-blood barrier, from the normal 1.5 to 3 μ after 3 days, was due primarily to enlargement of the interstitial space by accumulation of edema which was replaced secondarily by cells and fibrin. This was accompanied by destruction of about 50% of the capillaries. Morphometric data allowed an estimate of the degree of impairment of lung function. The primary cellular damage was located in endothelial cells which underwent cytoplasmic changes and, finally, fragmentation. In contrast, the damage to the epithelial lining of alveoli was relatively scarce compared to the extensive endothelial changes. This pertained even to severely damaged lungs with 65% of the alveoli obliterated by a heterogeneous exudate. Possible causes for this apparently different reaction of epithelium (the first target cell) and endothelium to toxic oxygen effects are discussed.

INTRODUCTION

It is one of nature's puzzling paradoxes that oxygen, essential for the support of life, is toxic when breathed for prolonged periods at partial pressures higher than normal. The type of damage depends on the partial pressure prevailing: at a pO_2 around 1 atmosphere (atm) the respiratory system appears to react first, while at higher pressures the primary disturbances are noted in the central nervous system. The use of pure oxygen atmospheres in aviation, diving, and space travel, as well as the introduction of oxygen high pressure breathing into therapeutics recently has revived interest in the mechanisms of oxygen poisoning (1–8).

The present study was undertaken to elucidate the nature and time-course of damage occurring in the lungs of rats breathing essentially pure oxygen at atmospheric pressure. Previous studies (9–24) had shown that disturbances in the alveolar space and capillary bed (25) were associated with damages, in lung tissues, which comprise accumulation of edema fluid and cells in the interstitial space, a thickening of the air-blood barrier, and changes in the fine structure of cells (26–28). While these findings, for the most part, were recorded in terminal phases of oxygen poisoning, the present study attempts to define the time-course of events from their inception to their final stages, by apply-

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ing methods of quantitative morphology and electron microscopy to a time series of oxygen exposure experiments.

In preliminary reports on this study (29, 30), emphasis has been placed on the functional aspects of damage to the lung as a gas exchange apparatus. The present report deals primarily with the cytological changes observed in the air-blood barrier, the tissue layer first exposed to the toxically elevated oxygen concentration.

MATERIAL AND METHODS

Experimental Animals

The present studies were conducted on young pure-bred male Sprague-Dawley rats born on the same day. 90 rats were divided into five groups; four test groups (1–4) which were sacrificed after 6, 24, 48, and 72 hr respectively, of exposure to a 98.5% oxygen atmosphere at 765 torr (Table I), and a control group (C) which was kept in room air until sacrifice under otherwise identical conditions.

Particular care was taken to eliminate from these groups all animals which showed any signs of murine pneumonia. Of the 90 rats, five thus had to be rejected (Table I).

Exposure to Oxygen

The test groups were brought simultaneously into an environmental chamber at the 6570th Aerospace Medical Research Laboratories, Wright-Patterson Air Force Base, Ohio. Technical design and facilities of this chamber have been described in detail elsewhere (31). A special study on a similar chamber (32) had failed to demonstrate the presence of any toxic contaminants under identical experimental conditions.

The chamber was supplied continuously with aviators' oxygen to maintain an average concentration of 98.5% oxygen throughout the experiments. It was pressurized 25 torr above ambient pressure, so that any possible leaks were outboard. The conditions prevailing in the chamber during the exposure period are shown in Table II.

TABLE I

Main Vital Characteristics of Rats Used

Group	Oxygen exposure	No. of animals	Age at sacrifice	Average body wt at sacrifice	No. of animals with murine pneumonia
	hr		*days*	*gm SD*	
C	—	14	44	123 ± 3	1
1	6	18	47	116 ± 1	2
2	24	17	48	119 ± 4	2
3	48	17	49	123 ± 4	0
4	72	24	50	102 ± 6	0

TABLE II

Characteristics of Chamber Atmosphere

Total ambient pressure, torr	765 (740 + 25)
Oxygen concentration, %	98.5 ± 1
Carbon dioxide concentration, %	Below 0.1
Relative humidity, %	46 ± 1
Temperature, °F	74 ± 2

± values: 1 standard deviation

Preparation of Lungs

At the end of exposure the animals of each group were anesthetized deeply by intraperitoneal injection of Nembutal (5 mg/100 g body weight), brought out of the chamber, weighed, labeled, and processed immediately in the following way: the trachea was exposed and opened, the chest was punctured to collapse the lungs, and a cannula was inserted into the tracheostomy. 2.5% glutaraldehyde, buffered to pH 7.4 with 0.03 M potassium phosphate, was instilled immediately at a standardized pressure of about 20 cm H_2O. The average time lapse between exit from the chamber and the start of instillation was 17 min, with a range from 4 to 35 min. After ligation of the trachea, the heart and lungs were removed en bloc from the chest and submerged in the fixative for 2 hr. Subsequently, heart and mediastinal tissue were dissected away carefully, and the lung volume was measured by fluid displacement.

Only lungs which were free of any signs of murine pneumonia and which were judged to be fixed perfectly were processed further. They were sliced with razor blades into alternately thick (3–5 mm) and thin (1 mm) slices.

The thick slices were embedded in celloidin-paraffin and prepared for light microscopy. The thin slices were cut into 200–300 small cubes of approximately 3 mm^3 which were washed for 2 hr in three changes of 0.11 M potassium phosphate buffer, post-fixed for 90 min in buffered 1% OsO_4, dehydrated in ethanol, and embedded in Epon (33). From the total pool of cubes of each lung, a random sample of 20 pieces was embedded into consecutively numbered blocks; the remaining material was bulk-embedded in plates as reserve. Sections of 2–3 mm^2 area and 600–900 A thickness were cut with a diamond knife, and picked up on 150-mesh copper grids fitted with a carbon-reinforced Formvar film. Section contrast

TABLE III

Sample Size for Morphometry

	No. per				Total No.
	Field	Section	Animal	Group	
Animals				5	25
Sections			5	25	125
Micrographs		6	30	150	750
Test points	168	1008	5040	25,200	126,000

was enhanced with lead citrate (34). The electron micrographs were taken in a Philips EM 200.

Lungs fixed in glutaraldehyde followed by OsO_4 regularly show a granular contamination along cell membranes. So far, we have not been able to eliminate this contamination which does not occur in other tissues fixed the same way. Therefore, a smaller number of randomly chosen lungs of each group were instilled directly with buffered 1% OsO_4 to serve as technical controls; further processing remained unchanged.

Sampling of Material

The glutaraldehyde-fixed and processed lungs were numbered consecutively in order of time of fixation. For morphometric work the first five lungs were selected. Of each lung, again the first five blocks were sectioned. Random sampling of six fields per section for electron micrography was done according to methods previously described, placing the screen into one specified corner of the selected mesh of the copper grid (35, 36). The size of the sample obtained by this procedure is shown in Table III.

For descriptive study of cellular changes the same material was used. In addition, for each group a smaller number of sections from lungs directly fixed in OsO_4 also were investigated. Comparison of the two preparations revealed no essential differences in fine structural changes; all electron micrographs reproduced here have been taken from OsO_4-fixed material for purely aesthetic reasons.

Stereologic Methods

The electron micrographs used for morphometric study were recorded on 35 mm film. Contact prints of the negatives were analyzed in a table projector unit, the screen of which was fitted with a multipurpose test system comprising 84 lines and 168 test points (36). The stereologic methods allowing an estimation of surface areas, volumes, and average thicknesses of tissue layers have been presented previously in detail (35–37). The statistical significance of the morphometric findings was tested by analysis of variance (38, 39).

RESULTS

General Observations

The first pathological changes were observed in animals removed from the chamber after 48 hr of breathing pure oxygen (group 3). They were dyspneic and, at autopsy, the normally pink and smooth lung surface was found to be mottled with small red and yellowish spots; the pleural cavity contained some exudate. These findings were exaggerated greatly in the last group of rats which remained in the oxygen atmosphere for 72 hr (group 4).

Light microscope preparations of the 6- and 24-hr groups (groups 1 and 2) revealed normal lung structure, while in group 3 a beginning formation of interstitial edema around some larger blood vessels could be observed. Lungs of group 4 showed striking changes in the alveolo-capillary region which were distributed focally over the whole lung: the interalveolar septa were thickened markedly and were rich in cells; alveoli were filled with a partly hemorrhagic exudate containing fibrin, numerous leukocytes, and macrophages. Morphometric analysis revealed that 65% of all alveoli were obliterated (29, 30), while about a third of the lung appeared normal in structure.

Morphometric Findings

Fig. 1 summarizes the essential morphometric findings which have been presented in detail else-

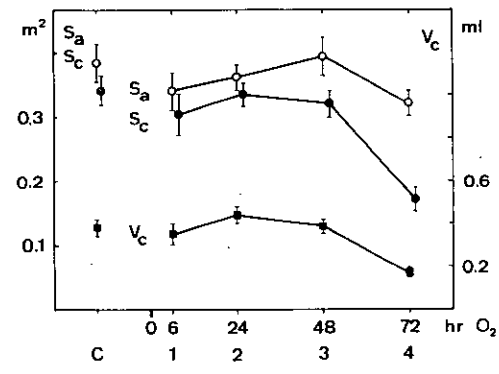


FIGURE 1 Alveolar surface area (S_a), capillary surface area (S_c), and capillary volume (V_c) in control rats (C) and during oxygen breathing for 6–72 hr. Brackets indicate standard errors of mean.

where (29, 30). The surface area of the alveolar epithelium (S_a) remained essentially unchanged throughout the entire experiment. The apparent reduction of S_a in group 4 was not found to be statistically significant.

In contrast, the capillary endothelial surface (S_c) and the capillary blood volume (V_c) fell, in group 4, to about 50% of their control values ($p < 0.01$), whereas no changes in these parameters could be detected at earlier time points. Comparison of Figs. 2 and 3 reveals that this can be explained by the destruction of capillaries within extended portions of interalveolar septa, accompanied by accumulation of leukocytes, fibrin strands, and cell debris in the tissue. In lungs of group 4, capillary blood occupied only 18% of the total septal volume as compared to 40% in the control lungs.

In the normal lung, the air-blood barrier, i.e. the tissue separating capillary blood from alveolar air, was estimated by a stereologic method to have an average thickness of 1.5 μ. As Fig. 4 shows, the average barrier thickness remained unchanged in groups 1 and 2, but increased to 2.1 and 2.9 μ in groups 3 and 4, respectively. It is evident from this diagram that this thickening is due essentially to a progressive enlargement of the interstitial space.

Normal Structure of Air-Blood Barrier

Since the structure of lung tissue in the normal rat has been described extensively in previous articles (40–43), only a few points essential for the present study shall be highlighted.

The tissue layers composing the barrier, capillary endothelium, alveolar epithelium, and interstitium are continuous throughout the lung (Fig. 2). The average thickness of the endothelium lining the capillary bed measures about 0.3 μ, that of the alveolar epithelium 0.65 μ, and that of the interstitium 0.55 μ (Fig. 4). From place to place, however, their thicknesses can vary considerably as is evidenced by Figs. 2 and 5–9.

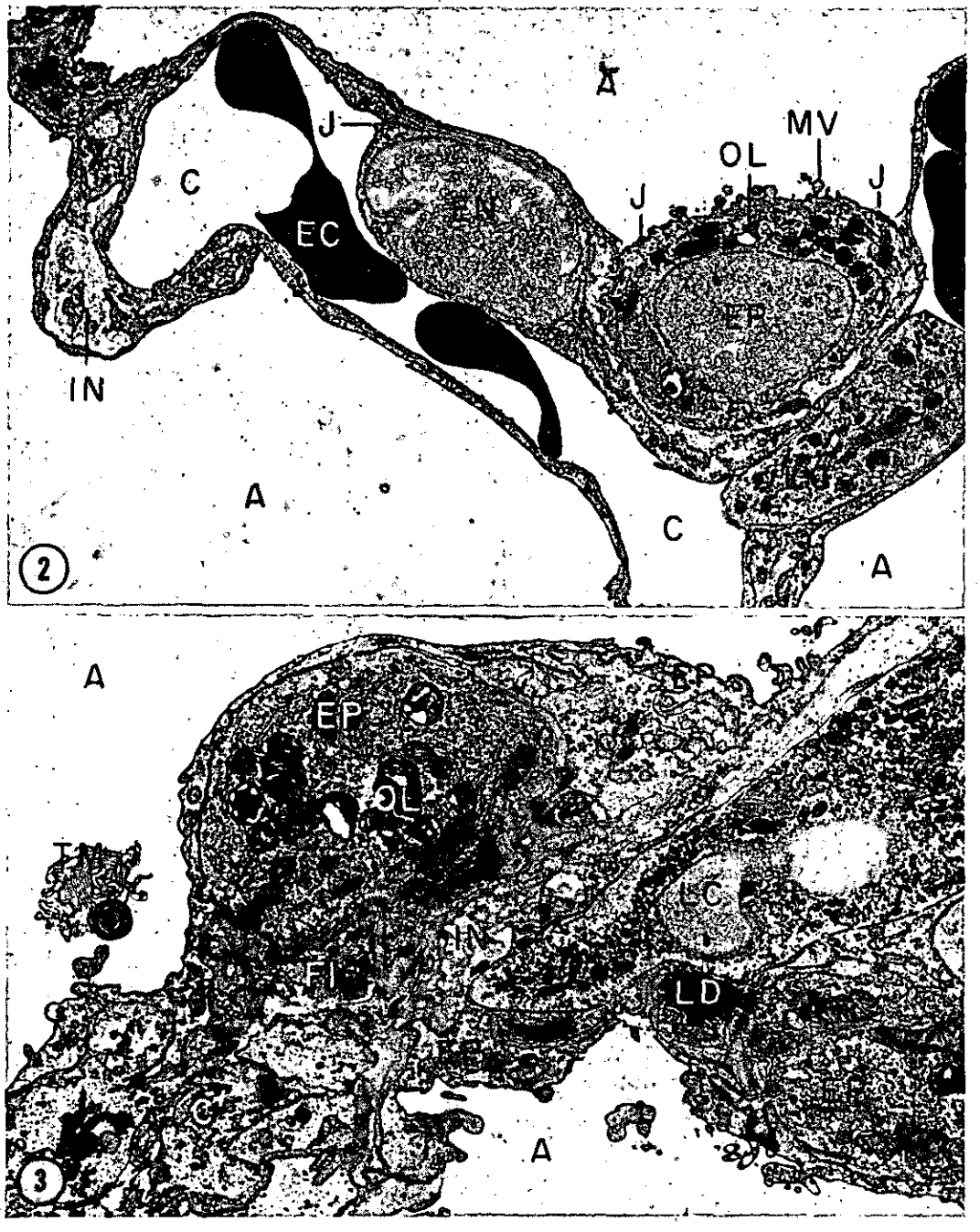
The endothelial cells form broad extensions of 0.1–0.5 μ thickness (Figs. 5 and 8). In some regions these can be attenuated to 250 A whereby only an extremely thin layer of cytoplasm separates the two cell membranes (Fig. 9). However, no pores or fenestrae can be found in these lung capillaries (44, 45 a.o.). Organelles are concentrated in the thicker perikaryon; the extensions contain only scarce and small mitochondria, scattered profiles of endoplasmic reticulum, and a few ribosomes. Micropinocytotic vesicles are numerous in all

Key to Symbols

A, alveolar space
BM, basement membrane
C, capillary lumen
CF, collagenous fibrils
EC, erythrocyte
ED, edema fluid
EF, elastic fibers
EN, endothelium
EP, epithelium
ER, endoplasmic reticulum
FB, fibroblast
FF, fine filaments
FI, fibrin
GO, Golgi vesicles
GS, ground substance space
IN, interstitium
J, intercellular junction
LC, leukocyte
LD, lipid droplet
MA, macrophage
MI, mitochondrion
MV, microvilli
N, nucleus
OL, osmiophilic lamellated bodies
T, thrombocyte
TM, tubular myelin figures

FIGURE 2 Normal interalveolar septum of control rat lung. Thick parts of air-blood barrier contain interstitial elements and cell bodies of endothelial and epithelial cells while thin barrier portions are formed by slim cytoplasmic extensions of epithelium and endothelium separated by fused basement membranes. × 5,900.

FIGURE 3 Interalveolar septum of rat lung after 72 hr exposure to oxygen. Note destruction of capillaries (*C'*) and remnants of endothelium, as well as leukocyte in interstitium. Tubular myelin figure in alveolar space. × 10,000.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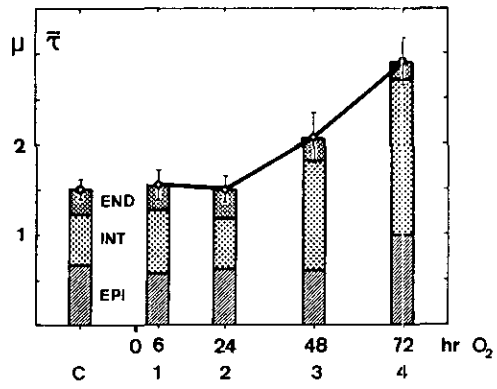


FIGURE 4 Change in average thickness $\bar{\tau}$ of air-blood barrier and of its composition in terms of endothelium (*END*), interstitium (*INT*), and epithelium (*EPI*). Brackets are standard errors of mean.

parts. The extremely attenuated portions (<1000 A) are entirely free of organelles (Figs. 8 and 9). At intercellular junctions the plasma membranes become closely apposed to each other in the luminal half of the contact zone (Figs. 5–8). As shown in Figs. 6 and 7 the gap between the osmiophilic layers is less than 100 A; there is a suggestion of a faint intermediate line, so that these appear to be zonulae occludentes (46). In their immediate vicinity the density of cytoplasm is increased slightly (Fig. 7).

The alveolar epithelium is composed of two cell types. The so-called small or type I alveolar cells are similar to endothelial cells with broad and thin extensions, and form the major part of the alveolar lining (Fig. 2). The distribution of cytoplasmic organelles and the structure of intercellular junctions correspond to that described above for endothelial cells (Figs. 5 and 8). The large alveolar epithelial cells (type II) have no extensions, but contain the characteristic, lamellated, osmiophilic granules (Figs. 2 and 24), (42, 47). Towards the alveolar lumen these cells form numerous, short microvilli. The junctions between large and small epithelial cells also contain a zonula occludens (Figs. 2 and 26).

The basement membranes of the epithelium and endothelium delimit the interstitium, which in some parts is reduced so far that the two basement membranes appear fused (Figs. 5, 6 and 9). In other parts the interstitial space is wider and contains fibroblasts, elastic fibers, and slim bundles of collagenous fibrils (Fig. 8). Some fine interstitial filaments are associated primarily with elastic fibers (Fig. 8). In view of the present study it is important to emphasize that the ground substance space of the pulmonary interstitium is very narrow in all parts of the air-blood barrier.

Structural Changes Observed after Oxygen Exposure

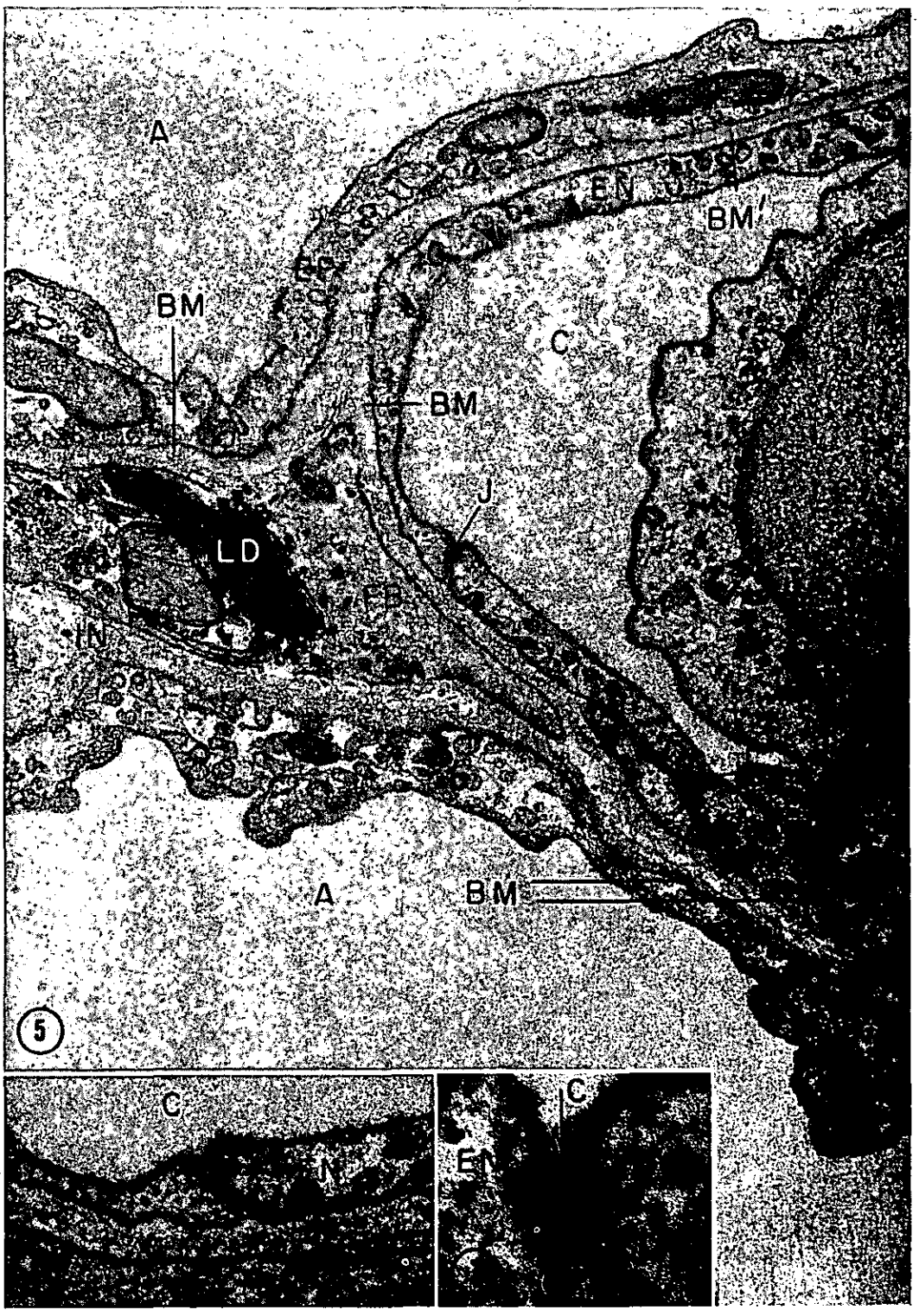
INTERSTITIUM: Fig. 4 indicates that the first changes in fine structure of the air-blood barrier become evident after 48 hr of oxygen breathing; they are recorded as an enlargement of the interstitial space from the normal 0.55 to 1.2 μ (Fig. 10). This thickening is statistically highly significant ($P < 0.01$) but earlier variations in thickness (group 1) are not significant. The widening of the interstitial space progresses during the third day of exposure to 1.7 μ on the average, i.e., to triple of control value.

A comparison of Fig. 11 with Figs. 2, 5, and 8 immediately reveals that in lungs of group 3, fluid has accumulated in the ground substance space of the interstitium. Epithelial and endothelial basement membranes, fibroblasts, and formed interstitial elements are separated by wide, empty spaces. The portions of the barrier in which epithelial and endothelial basement membranes are fused (Figs. 5 and 6) do not imbibe edema fluid (Fig. 11). 24 hr later, a peculiar granularity often appears over wide, edema fluid-filled spaces (Fig. 12). In other regions of group 4 lungs, numerous

FIGURE 5 Air-blood barrier of control rat lung with narrow interstitium. Note fusion of basement membranes (*BM'*) in thinnest portions. × 47,100.

FIGURE 6 Higher magnification of intercellular junction of endothelium in Fig. 5. Note close apposition of cell membranes in luminal half. × 85,600.

FIGURE 7 Demonstration of zonula occludens in junction of capillary endothelial cells. Note intermediate line (arrow) and condensation of cytoplasm near junction. Uranyl acetate and lead stain. × 186,000.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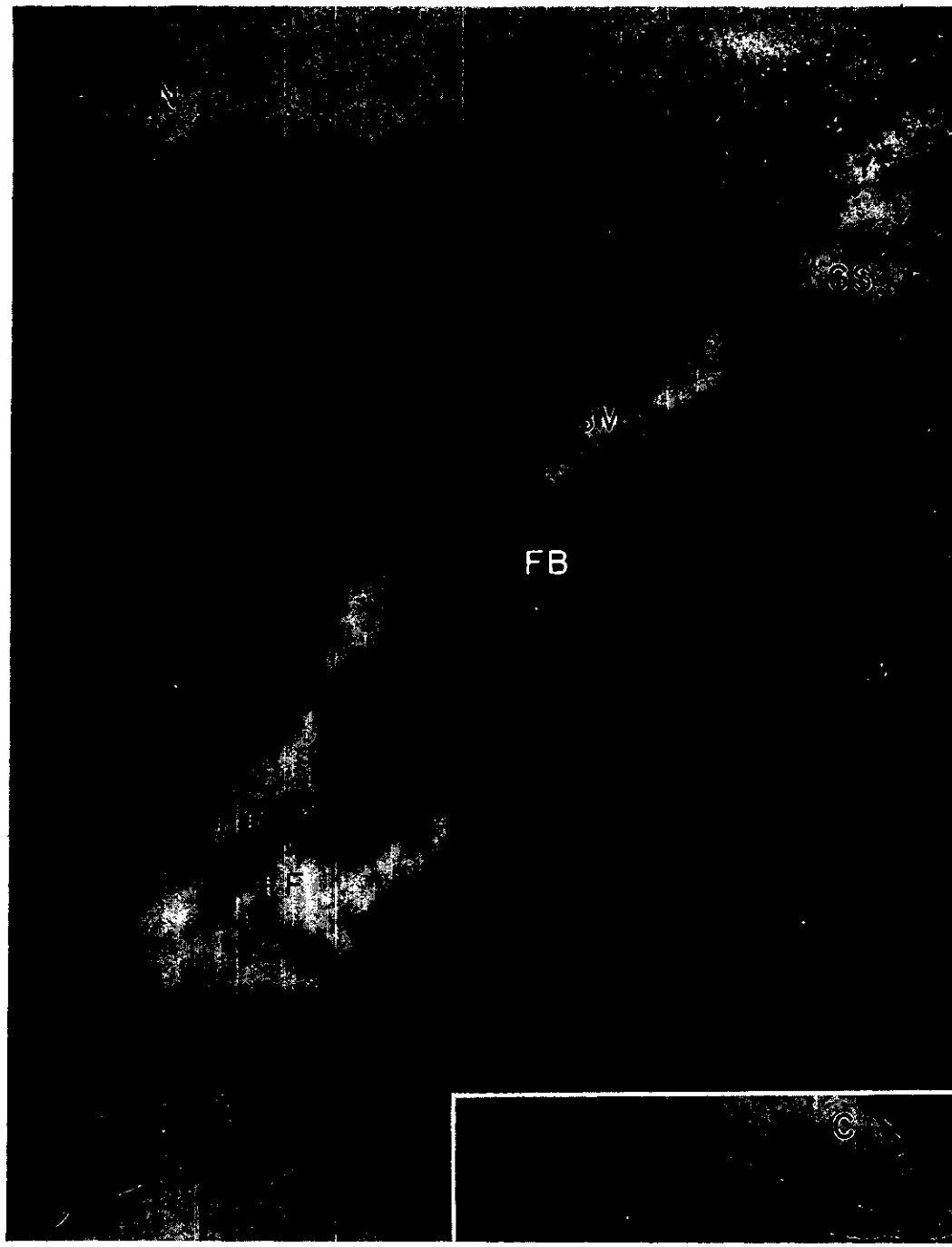


FIGURE 8 Thick part of air-blood barrier containing the various, formed elements of interstitium between endothelial and epithelial linings. × 57,800.

FIGURE 9 Extremely attenuated portion of endothelium. Note complete absence of organelles and single (fused) basement membrane between epithelium and endothelium. × 57,800.

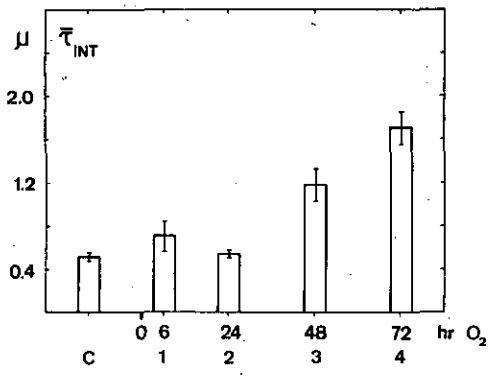


FIGURE 10 Change in average thickness of interstitial space. Brackets are standard errors of mean.

leukocytes and thrombocytes appear to have migrated into the interstitium (Figs. 3 and 13), and parts of the ground substance space contain fibrin strands (Figs. 21 and 23). Interstitial macrophages appear there and cell debris from destroyed blood vessels is present.

ENDOTHELIUM: The appearance of interstitial edema after 2 days of oxygen breathing suggests damage to endothelial cells. Morphometrically a statistically significant reduction of the average thickness of endothelium is detectable only after 3 days (Fig. 14).

Close examination of endothelial cells in groups 1 and 2 did not reveal any structural changes. In group 3 the vast majority of endothelial cells appeared entirely normal in structure, even in highly edematous areas of the barrier; in particular, the cell junctions were tight (Figs. 11, and 15). Peculiar changes occurred in scattered marginal regions of endothelial cells: the cytoplasm adjacent to intercellular junctions appeared slightly swollen, of often homogeneously increased density, and void of organelles (Fig. 16 and 17), while the junctions themselves were accentuated by augmented contrast (Fig. 17). These alterations in marginal cell structure also could be observed in group 4.

After 3 days of oxygen breathing, a large fraction of endothelial cells showed drastic changes. In Fig. 18 one of the cells lining the capillary is characterized by strikingly dark cytoplasm in which mitochondria, endoplasmic reticulum, ribosomes, and Golgi vesicles still can be recognized (Fig. 19). The junction with the adjacent cell is still tight; however, this obviously damaged cell is detached partially from its basement membrane. The lumen of this capillary contains thrombocytes and cell debris which is probably fragments of destroyed endothelial cells. Such fragments are also apparent on Fig. 17.

Fig. 20 reveals the varying picture of endothelial cell necrosis. Two profiles appear as empty, markedly swollen membrane sacs void of organelles; in others the cytoplasm is condensed and fragmented partially. Tight intercellular junctions can be recognized no longer. The endothelial basement membrane, however, is still intact. The capillary lumen contains no blood plasma. The hemoglobin of some red cell fragments is leached out partly.

Figs. 21 and 22 illustrate the final stage of endothelial cell destruction. The capillary is bounded exclusively by its basement membrane which is in direct contact with erythrocytes. Blood plasma is lacking and fibrin strands appear near the basement membrane.

EPITHELIUM: In spite of the drastic destruction of endothelial cells, the alveolar epithelium shows little change (Figs. 3, 18, 20–22). Even in group 4 the fine structure of the cytoplasm and organelles of the vast majority of small epithelial cells appears normal; interalveolar septa which contain only destroyed capillaries still may be covered by a seemingly intact epithelial lining (Figs. 21 and 22). In some rare areas, however, the entire barrier appears torn (Fig. 23), so that a continuity is established between blood vessels, interstitium, and alveolar space. Here it often can be observed that fibrin masses extend from the tissue space into exudate-filled alveoli.

The majority of large alveolar epithelial cells again shows normal fine structure even after 72 hr of oxygen exposure (Fig. 24). In some of these cells, however, a swelling of all membrane-bounded organelles, i.e. mitochondria, endoplasmic reticulum, perinuclear cisternae, and Golgi vesicles, is observed whereas the cytoplasmic ground substance is unaltered and is still rich in ribosomes (Fig. 25). In other instances the additional rarefaction of cytoplasmic ground substance appears to be due to imbibition of fluid (Fig. 26). The occurrence of cellular debris in alveoli after 72 hr (Fig. 20) suggests that such cells eventually may be destroyed.

Two-thirds of the alveoli of group 4 lungs were obliterated by a heterogeneous exudate which contained fibrin strands, cell debris (Fig. 20), and a peculiar myelin material (Figs. 3, 11, 27 and 28) which has been described in detail elsewhere (48).

FIGURE 11 Interalveolar septum after 48 hr of oxygen breathing. Note enlargement of ground substance space of interstitium by edema (*ED*). Compare with Figs. 2, 5, and 8. Alveolar and capillary linings apparently unchanged. × 18,300.

This material consists of spheroid bodies of concentrically arranged osmiophilic lamellae, possibly phospholipid in nature (48), which are associated with highly ordered structures. These exhibit a fingerprint-like pattern on section; stereologic analysis has shown that they are composed of densely, packed, square tubules of 450 A diameter that contain a fine inner tubule of 250 A. In some instances the inner tubule may be replaced by a thin central filament (Fig. 28), in which case the tubule diameter is 380 A (48). It should be noted that this material also is found in small quantities in normal lungs of many species (48–50), but never in masses as large as those observed here.

Besides leukocytes and erythrocytes, macrophages were numerous in the alveolar exudate; in Fig. 27 a macrophage is shown in the process of phagocytosing myelin material.

DISCUSSION

Time Sequence of Pathological Changes

The first changes detectable in lung tissue appear to develop during the second day of pure

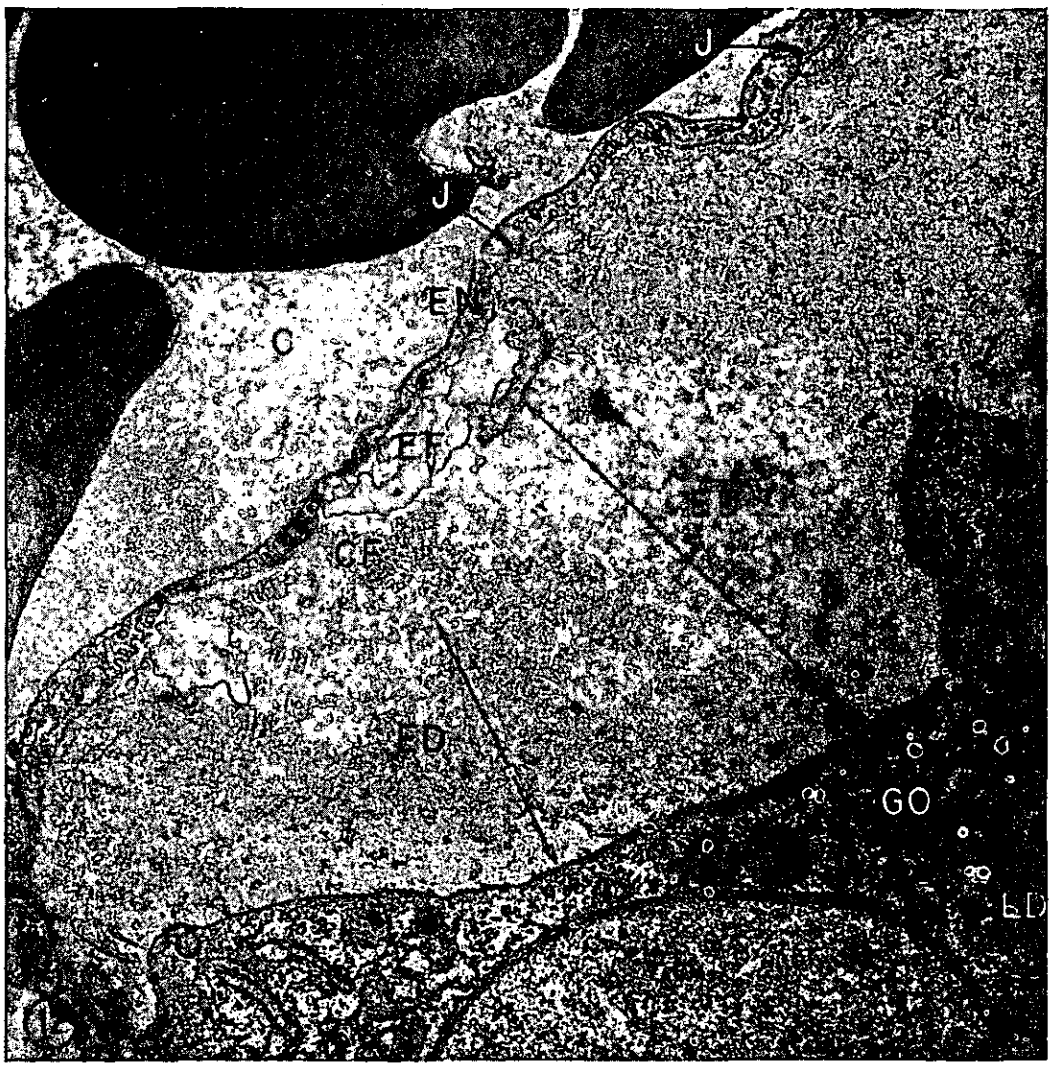


FIGURE 12 Edematous enlargement of interstitial ground substance space after 72 hr exposure to oxygen. Connective tissue fibers are separated from fibroblast by edema fluid showing granular precipitate of unknown nature. × 18 500.

FIGURE 13 Neutrophil granulocyte in interstitium of interalveolar septum after 72 hr exposure to oxygen. Epithelium and endothelium intact. × 21,800.

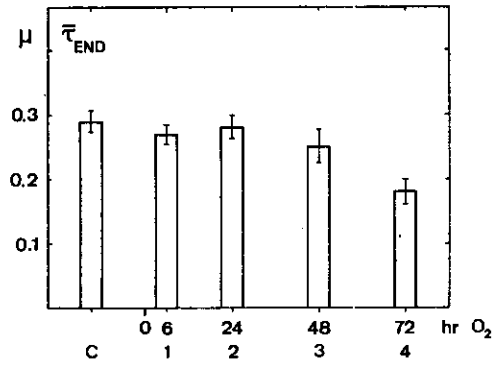
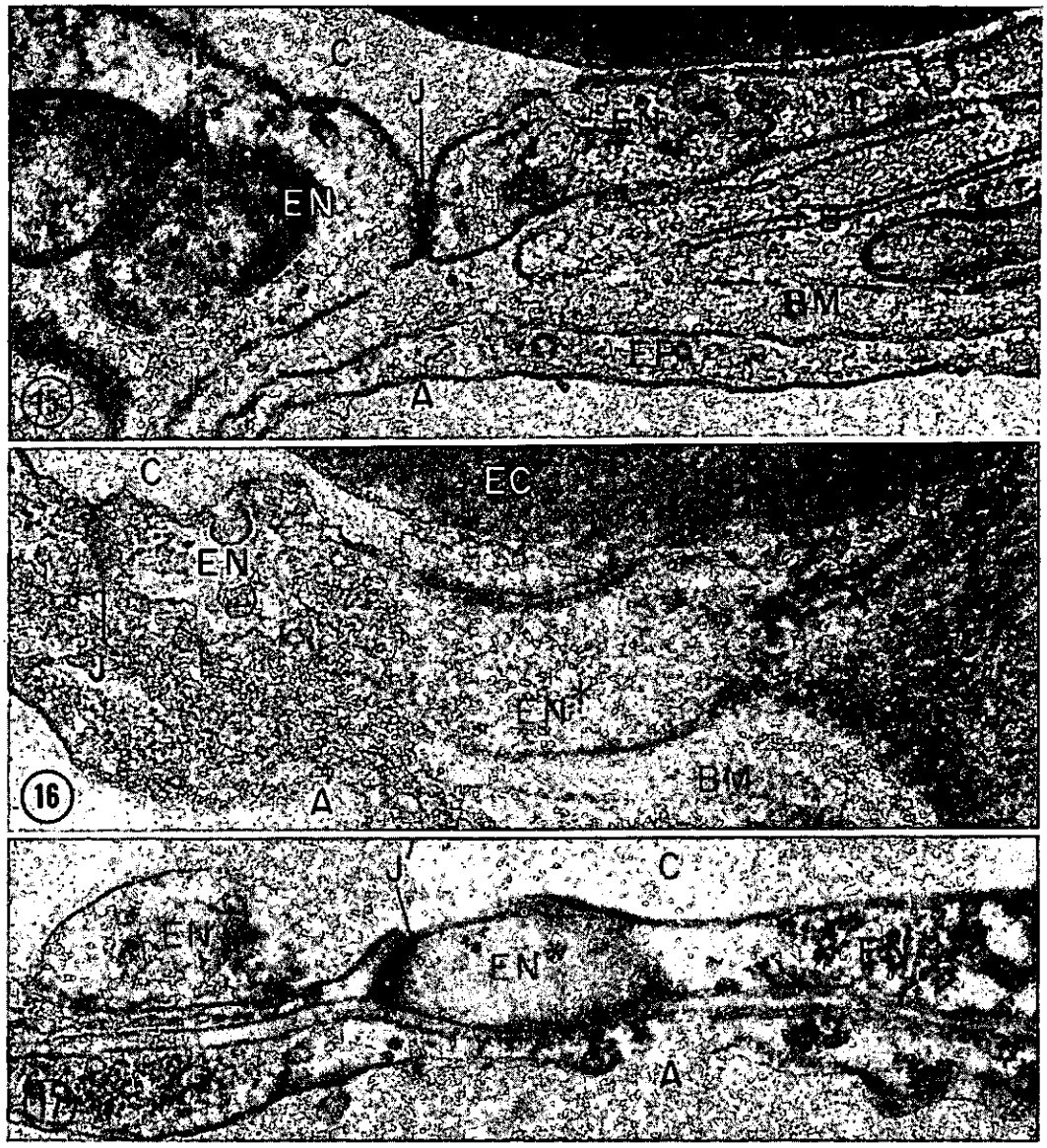


FIGURE 14 Changes in average thickness of endothelium. Brackets are standard errors of mean.

oxygen breathing and consist of edematous imbibition of the interstitial space. In light microscope preparations this is noted in the connective tissue sheath around some larger blood vessels. Electron microscopy revealed a progressive edematous enlargement of the normally slim interstitium of the alveolo-capillary air-blood barrier. It must be assumed, therefore, that the permeability of the capillary lining is increased, although only very minute and inconspicuous changes in fine structure of endothelial cells can be recognized at this stage.

During the third day a structural damage to endothelial cells develops, which results in complete destruction of the lining of a large fraction of



FIGURES 15–17 Marginal changes in endothelial cells after 48 hr exposure to oxygen.

FIGURE 15 Endothelium and junction apparently unchanged. × 69,900.

FIGURE 16 Granular condensation of marginal cytoplasm (*EN**); junctions unchanged. × 80,400.

FIGURE 17 Granular condensation and bulblike swelling of marginal cytoplasm free of organelles (*EN**) next to apparently normal cytoplasmic structure (*EN*). Capillary lumen contains cell debris of probably endothelial origin (EN^{+}). Contrast of intercellular junction (*J'*) accentuated. × 43,700.

the capillaries. This causes the capillary volume, as well as the capillary surface area, to fall to about 50% of the control values. Concurrently, leukocytes, macrophages, and thrombocytes, as well as fibrin strands, appear in the edematous interstitium. During the third day profuse exudation of a plasma-like fluid containing fibrin and numerous free cells obliterates up to two-thirds of the alveoli. This is accompanied by remarkably little damage to alveolar epithelium. In contrast to the massive destruction of capillary endothelium, the vast majority of epithelial cells show normal fine structure.

Progressive Impairment of Lung Function

The edematous thickening of the alveolo-capillary air-blood barrier, the loss of capillaries, and the obliteration of alveoli lead to an impairment of pulmonary gas exchange. In our experiments, this resulted in marked dyspnea, cyanosis, and asphyxia of the animals when these were brought back to room air after 3 days of pure oxygen breathing. This finding is consistent with observations made on other mammals and on man (9, 12, 15–18, 24, a.o.).

At earlier time points the animals showed no signs of asphyxia upon removal from the pure oxygen atmosphere. Nonetheless, pulmonary gas exchange must have been impaired already at the end of the second exposure day; calculation of a model value for the diffusing capacity of the barrier, from morphometric data, revealed that this parameter fell to 83% of the control value. During the third day the diffusing capacity thus estimated was reduced further to 25% (29, 30). The obliteration of two-thirds of the alveoli by edema fluid added to this functional damage; it was estimated that only some 10% of the original capacity of the lung for gas exchange remained available at this terminal stage. In experiments on human volunteers under equivalent conditions, Caldwell et al. (32) recorded a fall in pulmonary diffusing capacity to 81% of the control value after 48 hr and to 73% after 74 hr. Thus the measured drop in diffusing capacity in humans breathing pure oxygen correlates closely with the presently predicted fall in diffusing capacity of rats exposed to the same conditions. The fall in total lung capacity observed by these authors correlates with the obliteration of terminal air spaces by edema in our experiments.

Nature of Fine-Structural Changes

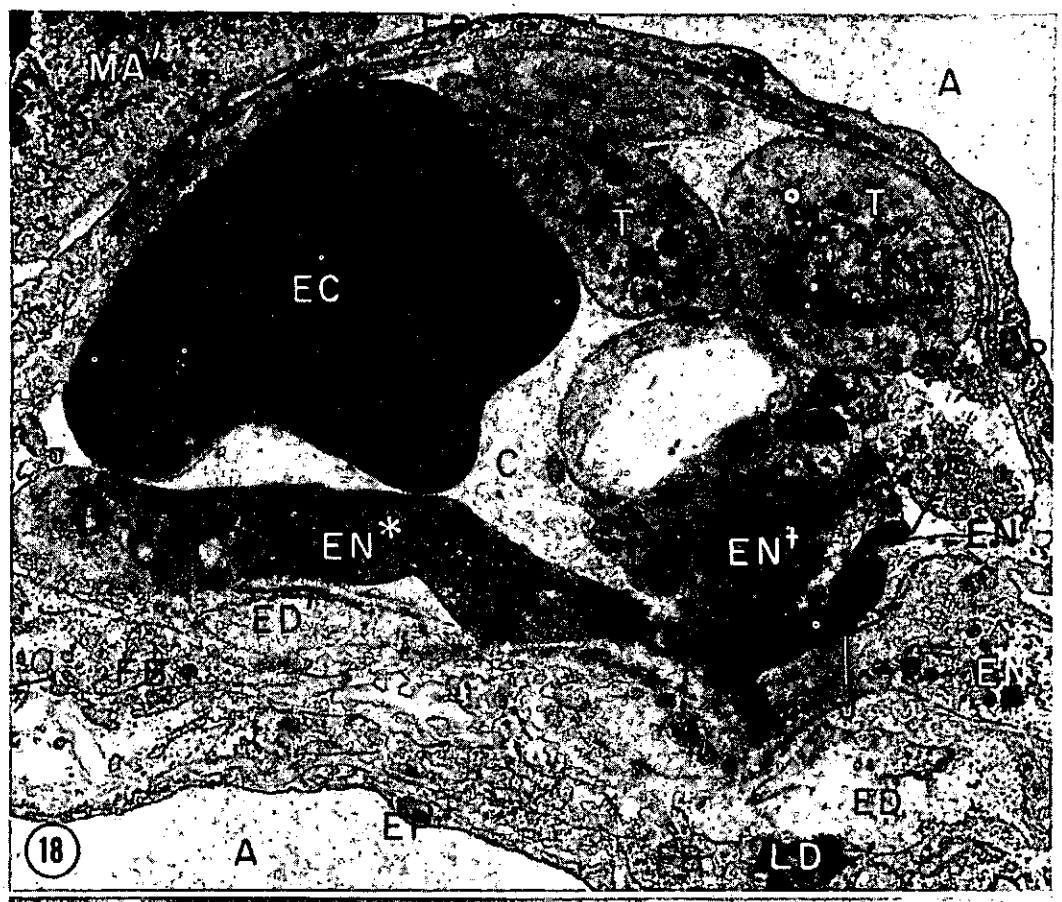
Most investigators agree that formation of interstitial and alveolar edema is a consistent finding in pulmonary pathology of severe oxygen poisoning (4, 10, 12, 15–17 a.o). This study has shown that interstitial edema of the pulmonary air-blood barrier develops while the architecture and fine structure of the lung seemingly are unchanged, and before any toxic effects on the organism become apparent.

This edema could form as a direct toxic effect of oxygen on some constituent of interstitial tissue, resulting in elevated osmotic pressure and swelling of the ground substance. Or, it may be the consequence of a primary vascular damage, for which two mechanisms can be imagined: (*a*) generalized spasm of small blood vessels, as found in the retina under the influence of oxygen breathing (51–53 a.o.), could cause elevated intracapillary pressure and movement of fluid into the tissue; (*b*) increased capillary permeability may be the result of direct injury to the endothelium.

While none of these possible causes can be excluded, the evidence presented in this study points to a local damage to endothelial cells as the primary cause for displacement of fluid, and eventually of cells, into the interstitium. In initial stages of edema formation, the endothelial lining of alveolar capillaries appears to be morphologically intact; the intercellular junctions are tight.

FIGURE 18 Alveolar capillary after 72 hr exposure to oxygen. Cytoplasm of one endothelial cell (*EN**) shows very marked electron-density; its junction with apparently unaltered neighboring cell (*EN*^{0}) seems intact. Note slight detachment from basement membrane (*ED'*). Capillary lumen contains thrombocytes (*T*) and cell debris of probably endothelial origin (*EN*$^+$). Alveolar macrophage (*MA'*) adjacent to unchanged alveolar epithelium (*EP*). × 15,800.

FIGURE 19 Higher magnification of "dark" endothelial cell in Fig. 18. Organelles are embedded in finely granular, dense cytoplasmic ground substance. Note edematous bleb (ED') between cell and basement membrane. × 46,700.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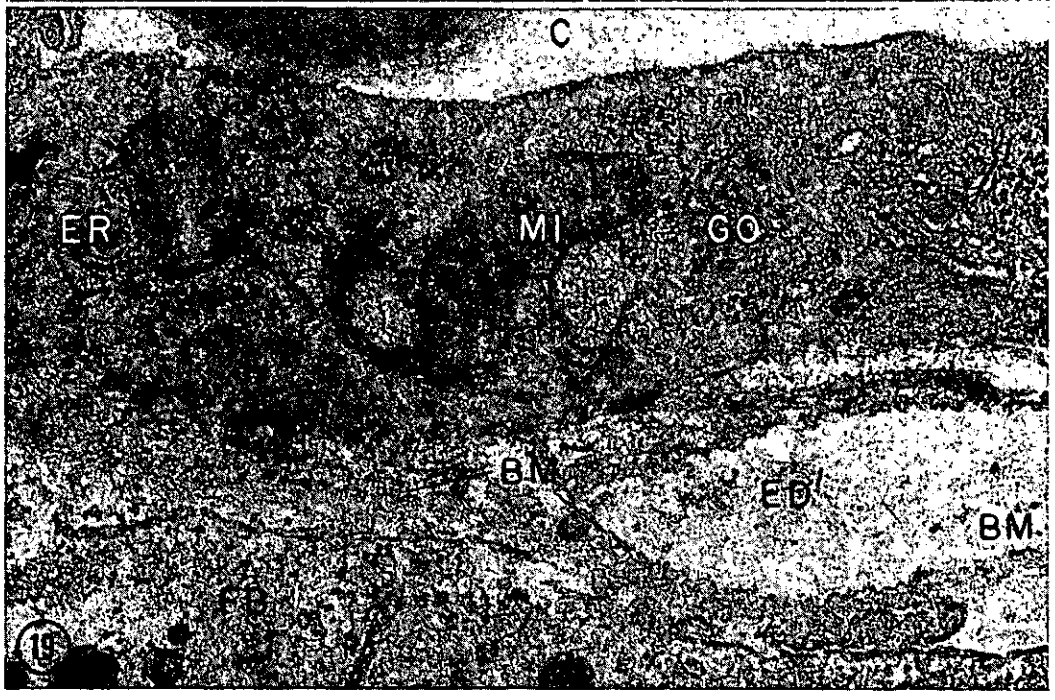
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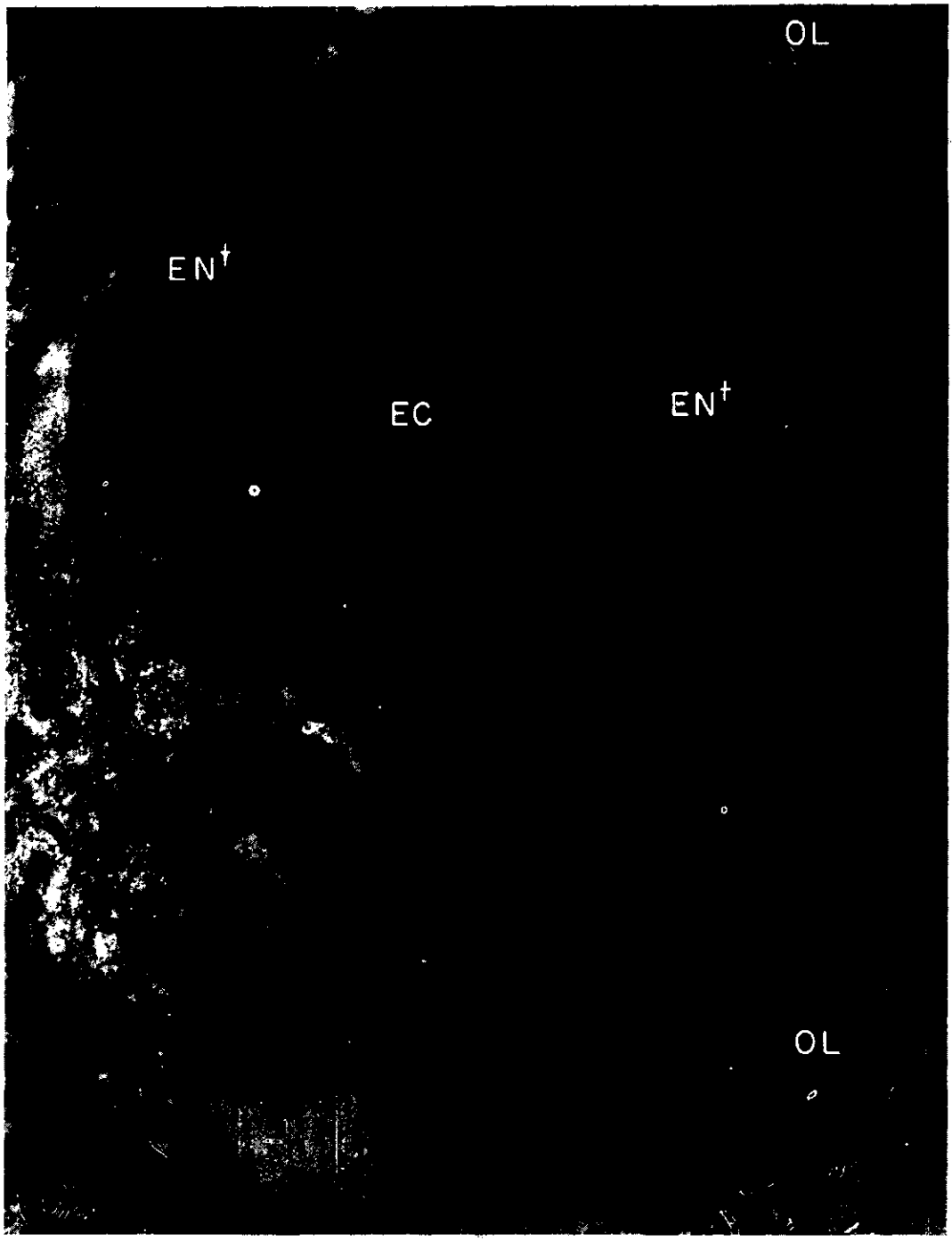
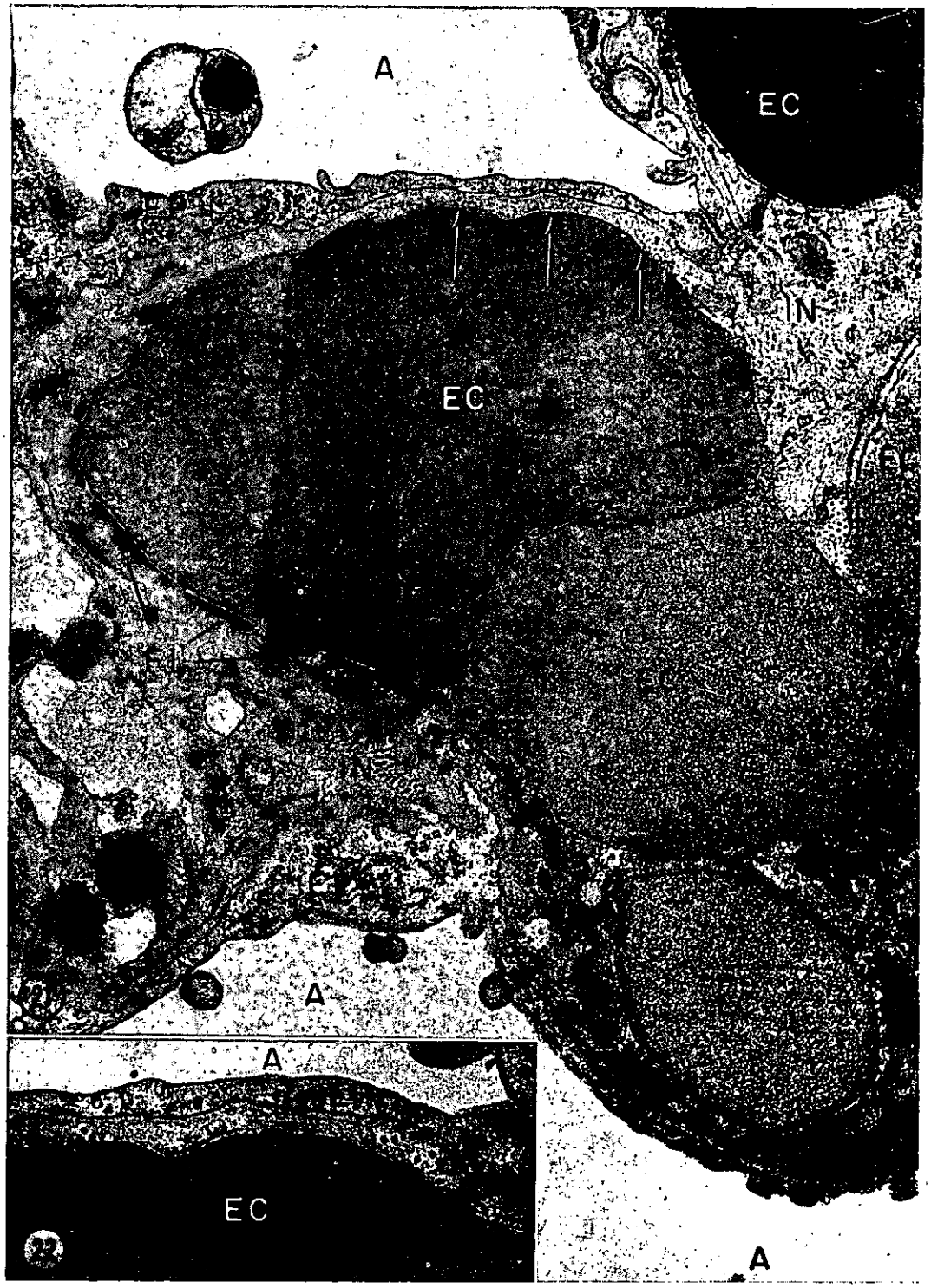


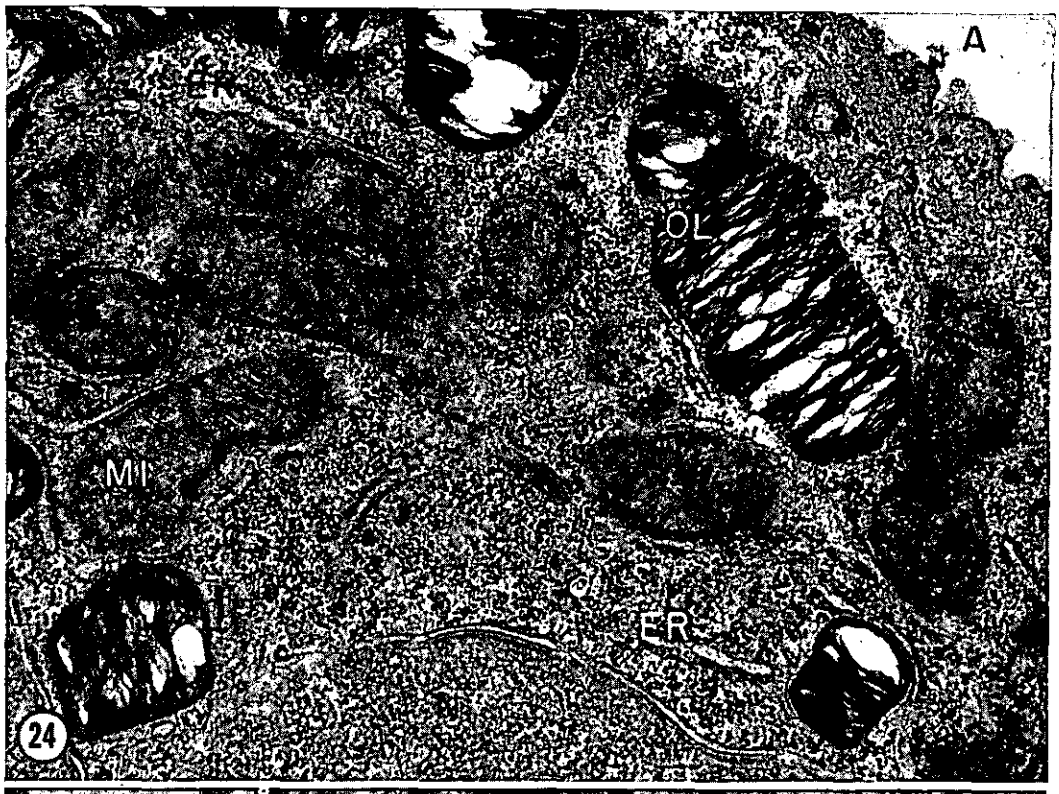
FIGURE 20 Alveolar capillary after 72 hr of oxygen breathing, showing different pictures of endothelial cell destruction: swollen cytoplasm free of organelles (EN^0), condensation of cytoplasm (EN^*), and fragmentation of cells (EN^+). Basement membrane is preserved. Epithelial lining still intact and of apparently normal fine structure. Alveolus contains cell debris of large alveolar epithelial cell (EP^+) with osmiophilic lamellated body (*OL*). Capillary lumen contains one seemingly normal red cell (*EC*) and various erythrocyte fragments (*EC'*) of varying electron-density. × 26,600.



FIGURES 21 and 22 Alveolar capillary after 72 hr exposure to oxygen has lost its endothelium. Tightly packed erythrocytes in former lumen are in direct contact with endothelial basement membrane (arrows), as is clearly shown at higher magnification in Fig. 22. Fine fibrin strands (*FI*) appear near basement membrane. Epithelial lining of alveolus intact. Fig. 21, × 16,500; Fig. 22, × 33,900.

Sparse marginal regions of endothelial cells show a peculiar change in cytoplasmic fine structure: a loss of organelles is accompanied, in part, by swelling and, in part, by granular condensation of cytoplasmic ground substance. This appears to initiate, during the 3rd day of oxygen breathing, the progressive destruction of endothelial cells which manifests itself in either swelling or granular condensation of cytoplasm followed by fragmentation. Previous cytological studies of oxygen effect on the lung (26, 27) have not emphasized this primary endothelial damage, although Cedergren et al. (28) mention vacuolar swelling of endothelial as well as epithelial cells. In our study, alveolar epithelial cells of both types showed remarkably few cytological changes even in regions with complete destruction of capillaries. Occasionally, swelling of mitochondria and cisternae of endoplasmic reticulum was observed in some epithelial cells of the large type. This well may be a secondary injury due to the heavy damage of surrounding tissues. Cytological changes described

FIGURE 23 Disruption of air-blood barrier (arrows) in alveolar capillary after 72 hr of oxygen breathing. Condensed remnants of endothelial lining (EN^*) and fragmented cells (EN^+) mark former capillary lumen. Note fibrin strands (FI) in capillary lumen and interstitium. × 32,600.



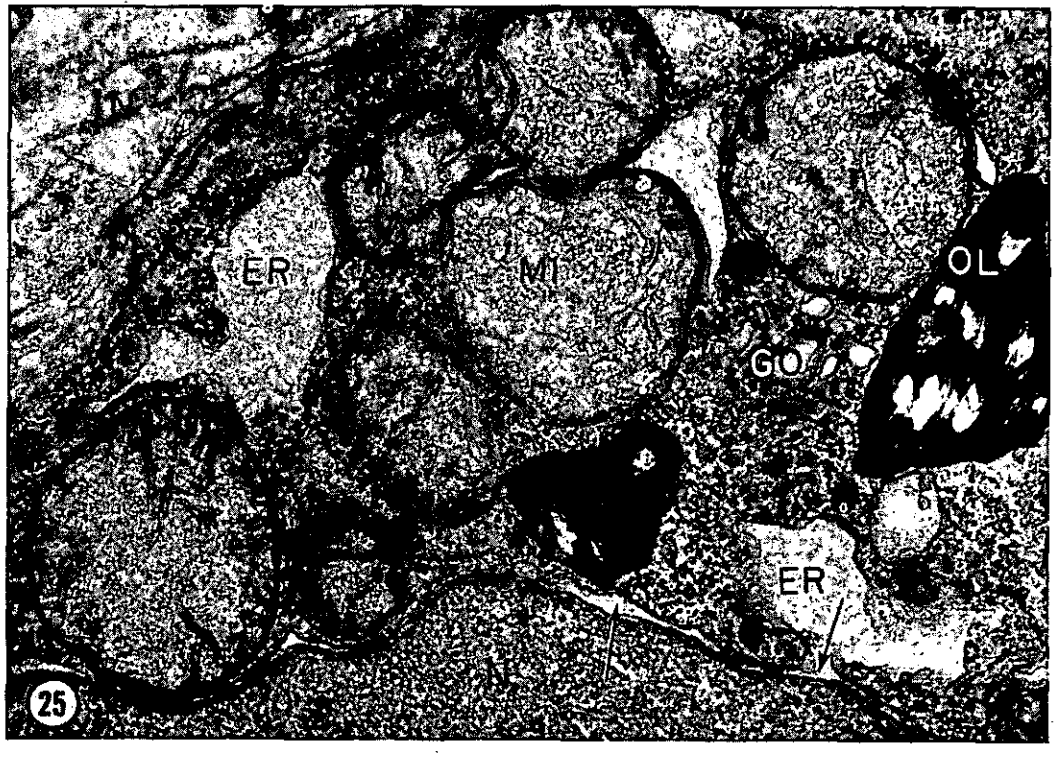


FIGURE 24 Large alveolar epithelial cell with osmiophilic lamellated bodies after 72 hr exposure to oxygen. Normal appearance of cytoplasmic structures. × 34,000.

FIGURE 25 Large alveolar epithelial cell from same lung as Fig. 24. Note swelling of mitochondrial matrix, of cisternae of endoplasmic reticulum continuing into perinuclear cisterna (arrows), and of some Golgi vesicles. Ribosome content of cytoplasmic ground substance unchanged. × 34,000.

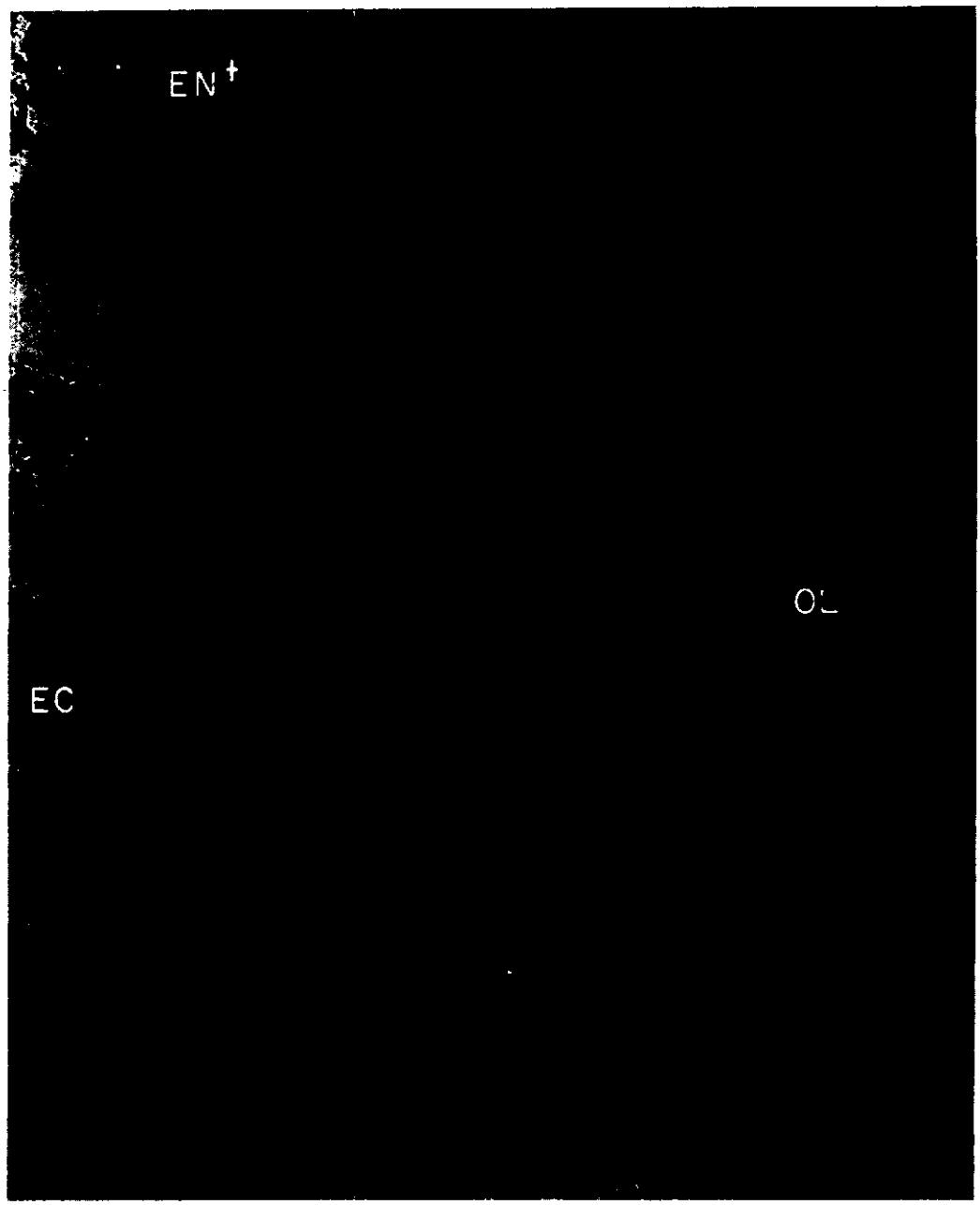


FIGURE 26 Large alveolar epithelial cell after 72 hr exposure to oxygen. Pronounced swelling of membrane-bounded organelles, particularly of cisternae of endoplasmic reticulum (*ER*). Major part of cytoplasmic ground substance exhibits edematous imbibition. Cell membrane and intercellular junctions are intact. Note destroyed capillary endothelium (*EN** and *EN*+). × 21,800.

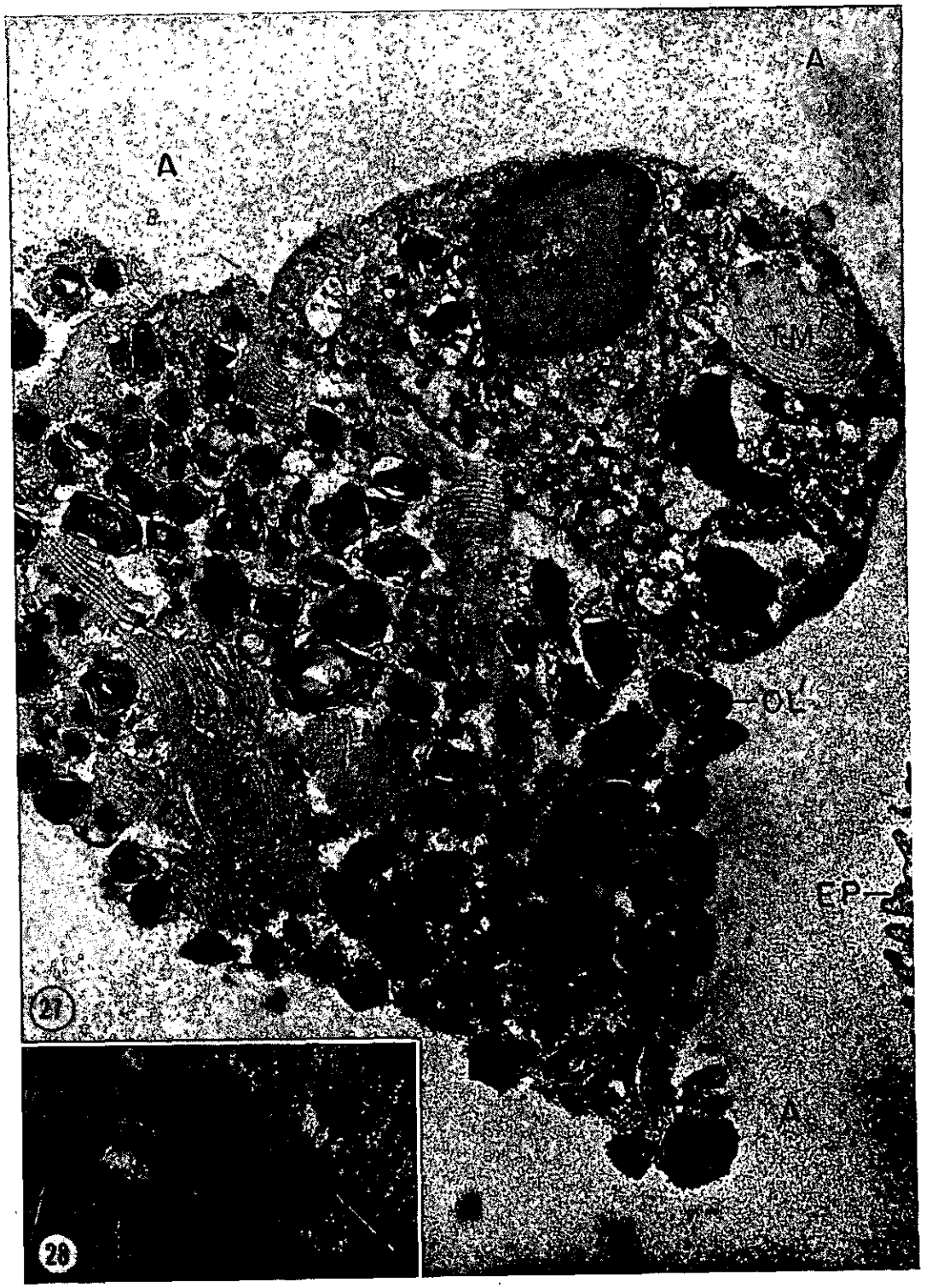


FIGURE 27 Mass of tubular myelin figures (*TM*) and lamellated osmiophilic spheroids (*OL'*) from alveolar exudate in lung after 72 hr exposure to oxygen. Macrophage (*MA*) is in process of phagocytosing this material (*TM'*). × 13,800.

FIGURE 28 Tubules of peculiar "myelin figures" are packed densely in square lattice and contain fine inner tubule or central filament (arrows), as shown in longitudinal and transverse sections. × 71,800.

for other organs (54) are difficult to correlate with the present pulmonary findings.

Specificity of Toxic Oxygen Effect

In various studies (55–57) the supplementary role of factors other than oxygen for the development of the oxygen toxicity syndrome is stressed. Among these, high pCO_2 levels appear to be most important; in the present experiments, CO_2 concentration was kept below 0.1 % so that this factor can be excluded. Contaminants, particularly pulmonary irritants, were not found in the chamber atmosphere. Since the experiments were conducted at sea level pressure, no barometric effects must be assumed. Therefore it can be safely concluded that the effects observed are related to the high partial pressure of oxygen in the medium breathed. It may be interesting to mention, in this context, that the breathing of pure oxygen at ⅓ atmosphere during a 2 wk period produced no similar morphologic changes in the lung tissue of identical rats (58).

The present experiments were conducted on nonpathogen-free, young Sprague-Dawley rats. It appears that sensitivity to elevated oxygen concentrations varies considerably among different species, as well as between strains of the same species (59, 60). Sprague-Dawley rats were selected for this study because of their rapid development of pulmonary changes. It also appears that pathogen-free animals are less susceptible than regular stocks (59, 60). This may indicate that oxygen alone cannot produce toxic effects but that additional (endogenous) factors play an essential role, a point to which reference will be made below.

Remarks on Possible Mechanism of Oxygen Effect on Cells

Breathing pure oxygen at 1 atm. ambient pressure causes severe damage to lung tissue and is found to gravely impair lung function. The change is progressive and eventually leads to asphyctic death. The present study has localized the primary injury in endothelial cells of alveolar capillaries and has explained the other changes as its consequence. It would be tempting to speculate on the specific cytotoxic mechanisms involved in endothelial cell damage; inhibition of enzymes, formation of lipid peroxides, and other biochemical disturbances have been suggested as playing an eminent role (see reference 57). However, it is not possible to interpret conclusively our present data in terms of these biochemical findings.

The most puzzling observation relates to our finding that endothelial cells are damaged first by an agent that has to traverse a similar tissue layer before reaching its target. The question why epithelial cells, which are directly exposed to the high oxygen pressure, are not damaged, whereas endothelial cells undergo such early and drastic changes, remains unanswered. It may be proposed that oxygen can exert its cytotoxic effect only in the presence of additional factors; this is suggested from studies on enzyme inhibition by oxygen, which depends on contamination of the preparations by various compounds (see reference 57). If such factors are endogenous and can be supplied by the blood, endothelial cells of alveolar capillaries could be regarded as the site of most intense interaction between oxygen coming from alveolar air and "additional factors" supplied by capillary blood. This possibility is being investigated further.

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Oxygen Toxicity. Effects in Man of Oxygen Inhalation at 1 and 3.5 Atmospheres Upon Blood Gas Transport, Cerebral Circulation and Cerebral Metabolism[1]

C. J. LAMBERTSEN,[2] R. H. KOUGH, D. Y. COOPER, G. L. EMMEL, H. H. LOESCHCKE[3] AND C. F. SCHMIDT. *From the Laboratory of Pharmacology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania*

SINCE PAUL BERT first demonstrated that generalized convulsions can be produced by prolonged inhalation of oxygen at pressures greater than 1 atmosphere (1), the paradox of central nervous system intoxication by an excess of this essential gas has stimulated much experimentation and debate. The extensive pertinent literature has been reviewed by Stadie, Riggs and Haugaard (2) and by Bean (3) and will not be recapitulated here. It must suffice to point out that the occurrence of generalized convulsions, if the oxygen pressure and duration of exposure are sufficiently great, and that the requisite length of exposure varies as an inverse function of the partial pressure of oxygen breathed, are well established in man (4–7). The cause of the convulsions however remains uncertain and at present the explanation appears to rest in one or more of the following: *a*) a direct toxic effect of high oxygen pressures upon certain constituents of brain cells; *b*) an accumulation of carbon dioxide in toxic quantities in the central nervous system because of breakdown in the normal transport function of hemoglobin for this gas; *c*) changes in the cerebral circulation.

There is a certain amount of evidence to support each of these but it is insufficient to establish any of them as the sole factor responsible for oxygen convulsions. Direct poisoning of brain cells has been frequently demonstrated (8–10) in tissues exposed *in vitro* to oxygen at pressures ranging from 1 to 8 atm. and Stadie and his co-workers (11–14), Dickens (15) and Haugaard (16) have presented evidence which indicates that cellular enzymes which depend on labile sulfur are particularly susceptible. The criterion of the toxic effect of oxygen was usually diminution of the rate of

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[2] John and Mary R. Markle Scholar in Medical Science.
[3] Rockefeller visiting fellow from Dept. of Physiology, University of Göttingen, Germany.

oxygen uptake by the tissue *in vitro* and to bring this about in the brain the exposure had to last considerably longer than the usual latent period for oxygen convulsions in intact animals exposed to the same pressure of oxygen (17). Furthermore, it is difficult to reconcile depressed oxygen uptake by the brain with generalized convulsions, for according to available information the latter typically entail an increase in the oxygen consumption of the brain *in vivo* (18–20).

Accumulation of carbon dioxide in the tissues as the result of 'breakdown in co-ordination of the dual function of hemoglobin' during oxygen inhalation at pressures higher than 3 atm. was postulated by Gesell (21). He considered that if the amount of oxygen carried in physical solution by the blood at such pressures was sufficient to meet existing metabolic requirements, oxyhemoglobin would circulate unchanged through the tissues. This would deprive hemoglobin of an important function, namely the release of base which normally permits the transport of carbon dioxide from the tissues with minimal changes in hydrogen ion concentration and pCO_2 in the blood. On this basis it has been repeatedly proposed that an increase in carbon dioxide tension in the brain plays an important role in producing acute oxygen poisoning (3, 18, 21–23).

This proposal is supported by four types of experimental evidence. First, extremely high carbon dioxide pressures (more than 300 mm. Hg in some cases) have been found in gas or liquid depots introduced subcutaneously or intraperitoneally in animals breathing oxygen at 3.5 to 5 atm. (22, 24, 25). Second, a rise in the acidity of venous blood has been reported in dogs exposed to high oxygen pressures (23). Third, inhalation of carbon dioxide in low concentrations is known to shorten markedly the latent period prior to the onset of convulsions when oxygen is breathed by small animals or man under high pressures (24, 26, 27). Muscular exercise has a similar effect (6, 7), which is regarded as further support for this conception. Fourth, inhalation of carbon dioxide in amounts (about 30% at sea level), sufficient to produce arterial tensions of the gas approaching those reported in gas depots in animals displaying oxygen convulsions, is well known to produce generalized convulsions in man (28).

Only one attempt apparently has been made to demonstrate this effect on carbon dioxide transport by appropriate analyses of the blood of animals breathing oxygen under increased pressure. In this study, made on anesthetized dogs, Behnke, Shaw, Shilling, Thomson and Messer (29) found that inhalation of oxygen at 3.8 atm. raised the pCO_2 of the mixed venous blood by an average of 6.5 mm. Hg above the value found during air breathing at sea level. This rise, while not of the same order of magnitude as that reported from the gas and fluid equilibrations *in vivo*, is not insignificant physiologically because it approximates the elevation in cerebral venous pCO_2 to be expected from breathing nearly 7 per cent carbon dioxide at normal barometric pressure (30–32). Since, however, no symptoms resembling oxygen convulsions are encountered during the latter procedure it is unlikely that such an accumulation of carbon dioxide in the brain could in itself be a satisfactory explanation of oxygen poisoning. Furthermore, Stadie *et al.* (8) and Dickens (9) could demonstrate no increase in the susceptibility of brain tissue slices to the toxic effects of high oxygen pressures upon the addition of carbon dioxide. The evidence for a direct relationship of carbon dioxide to oxygen poisoning is therefore somewhat ambiguous.

Changes in the cerebral circulation have long been included among the contributory factors in oxygen toxicity but there has been no agreement as to even the direction of the change to be expected. Dautrebande and Haldane (33) assumed the

effect of high pO_2 to be vasoconstrictor and conceived of this as a mechanism for minimizing the pO_2 to which the brain cells are exposed. Bean (3) on the other hand believed that retention of carbon dioxide at high oxygen pressures would lead to cerebral vasodilatation and thus to an even greater rise in brain tissue pO_2 than would have occurred otherwise. The available evidence favors the view of Dautrebande and Haldane. Constriction of cerebral blood vessels on breathing oxygen at 1 atm. has been reported by Wolff and Lennox (34) and Schmidt (35) with two different methods in cats, by Dumke and Schmidt (36) with another method in monkeys, and by Kety and Schmidt (30) with still another method in man. The latter study showed an average rise in cerebral vascular resistance of about 35 per cent when oxygen was breathed instead of air by normal men at sea level. If the cerebral vasoconstriction were to progress as a direct linear function of the prevailing arterial pO_2 it could become a factor of importance in oxygen toxicity by bringing about a significant cerebral ischemia at the pressures required to elicit convulsions.

The experimental data summarized above and reviewed in detail elsewhere (2, 3) indicate a continued uncertainty regarding the cause (or causes) of oxygen poisoning and even the pattern of the poisoning. This is largely because most quantitative studies at pressures greater than 1 atm. have been carried out on animals other than man and under conditions (anesthesia, excision of tissue) more or less remote from the normal even in those animals. The adaptation for use at increased ambient pressures of quantitative methods for measuring the pH, gas contents and tensions of arterial and cerebral venous blood, as well as the rate of cerebral blood flow and oxygen consumption, placed in our hands a means for evaluating in man all three of the major proposals noted above. The present study was undertaken in hopes of accomplishing this. It consisted of three separate series of experiments, each performed upon a different group of subjects. They are designated *group I*, *II* and *III* in the remainder of this report. The measurements upon *group I* were carried out at the beginning and end of a 1-hour period of air breathing at normal atmospheric pressure in order to establish the range of spontaneous variation to be expected in the factors under investigation. *Group II* was used for observations of the effects of oxygen inhalation at sea level and was therefore studied just before and 1 hour after such inhalation was initiated. Only *group III* was exposed to oxygen at increased ambient pressure. After the initial control measurements during air breathing at 1 atm., oxygen was administered for 10 minutes to speed the removal of inert gas from the blood and then, with the subject still breathing oxygen, compression was begun. Approximately 20 minutes were required to reach the desired pressure and 20 minutes later the withdrawal of the blood samples was completed. The majority of experiments in *group III* were performed at 3.5 atm. of oxygen, the highest inspired oxygen tension which would in most instances permit completion of the sampling procedures before the onset of convulsions.

Methods

The experiments were carried out in a steel chamber large enough to accommodate a subject and a team of four investigators, all of whom were exposed to the same ambient pressure. Temperature within the pressure chamber was maintained within the range of 20° to 25°C. by means of a thermostatically-controlled cooling system; the marked rise in temperature ordinarily associated with compression of air thus was obviated. During the experimental periods at 3.5 atm. the maximum variation of pressure within the chamber was ±0.3 psi. Each of the 33 normal men

(age 18–37 years) who served as subjects had been indoctrinated into the sensations of compression on a day prior to the actual experiment. They reported to the laboratory at 8:00 A.M. without having had breakfast and rested in a supine position for about 1 hour before the experiment was begun. During the first half of this period all the necessary preparations, including vascular punctures, were completed.

For estimation of cerebral blood flow, cerebral oxygen consumption and cerebral vascular resistance the nitrous oxide method of Kety and Schmidt (37) was used with minor modifications designed to overcome the difficulties peculiar to performing these measurements at increased ambient pressures. The concentrations of nitrous oxide used were 15 per cent with 21 per cent oxygen and 64 per cent nitrogen for control measurements at normal inspired pO_2, 15 per cent and 4.5 per cent in oxygen for studies of the effects of high oxygen tensions at 1 and 3.5 atm., respectively.

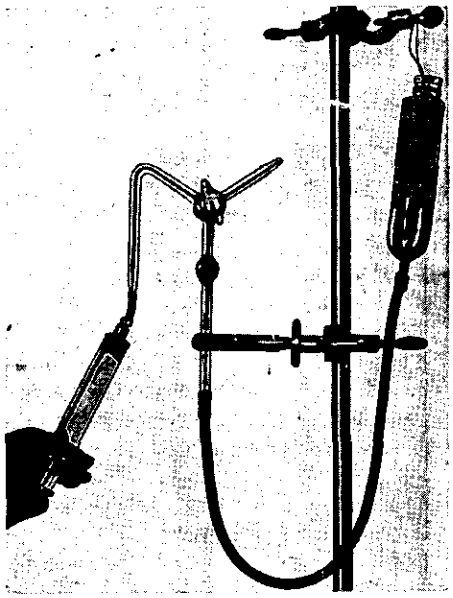

Fig. 1. ANAEROBIC PIPETTE used for blood samples collected at high barometric pressures.

During the stabilization periods commercial compressed air or oxygen (99.4%) was administered by means of a system comprising a mouthpiece, nose clip, breathing valves and a demand regulator attached to a cylinder of the desired gas. During the phases of the experimental procedure when nitrous oxide-containing mixtures were used an excessive gas flow into an 8-liter rubber bag replaced the demand regulator.

Blood samples were collected through 19-gauge needles inserted into a femoral artery and the right internal jugular bulb following infiltration with 2 cc. of 2 per cent procaine solution. The needles were left in place and connected to heparin-filled manifolds of three-way stopcocks[4] to which several 10 cc. glass syringes could be attached for ease and speed of sampling. The syringe dead space (average 0.2 cc.) was filled with commercial heparin solution. Extreme care was used to remove all trapped air bubbles from the syringes and collecting system prior to sampling. To

[4] Made by Mr. D. W. T. Cochrane of this laboratory (see 37).

minimize the dilution error each syringe was flushed with 2 cc. of the subject's blood immediately before the actual collection was begun. This procedure was omitted for specimens on which only nitrous oxide determinations were to be made. In order to avoid forcing an air bubble into the syringe all blood samples were capped with hypodermic needles which were inserted into rubber stoppers after the needle lumen was filled with blood. Samples withdrawn at normal atmospheric pressure were immediately placed in ice-salt mixture and processed in the usual way. When collections were made under higher pressures, blood for subsequent gas content determinations at sea level was transferred to calibrated, 1 cc. anaerobic pipettes (fig. 1) before the chamber pressure was lowered. These were also iced. Thus any gas which evolved from the sample during decompression remained trapped in the anaerobic pipette and was delivered into the analytical aparatus along with the accurately measured volume of blood from which it came.

The carbon dioxide and oxygen contents of the blood samples were determined manometrically by the technique of Van Slyke and Neill (38) and nitrous oxide content by Kety's modification of the method of Orcutt and Waters (37, 39). Duplicate analyses were done routinely; those for carbon dioxide and oxygen content were completed within 2 hours, those for nitrous oxide within 7 hours of the time of collection. Hemoglobin concentration in blood was estimated spectrophotometrically as cyanmethemoglobin (40) and oxygen capacity was calculated from this on the assumption that 1 gm. of hemoglobin combines chemically with 1.34 cc. of oxygen (41). The analyses were made in duplicate on 0.2-cc. samples diluted 1:250 and read at a wave length of 540 mμ. In separate experiments to determine the accuracy of this method we could detect no significant difference between the results of such determinations and direct measurements of oxygen capacity by the Van Slyke manometric method on the same blood samples.

The oxygen tensions of blood samples that were not totally saturated with oxygen were estimated from the dissociation curves of Bock (42) after the oxygen saturation and pCO_2 had been determined. When oxygen tensions high enough to produce 100 per cent saturation were used, the blood pO_2 was calculated from the oxygen physically dissolved (estimated by subtracting the hemoglobin oxygen capacity from the observed total oxygen content) and the solubility coefficient for oxygen in blood at 37°C. (43). While the procedure entails an error of approximately ±100 mm. Hg this is only about 5 per cent of the arterial oxygen tension (average 2100 mm. Hg) encountered when oxygen is breathed at 3.5 atm.

In order to avoid alteration of pH by loss of gas on decompression, estimations of the pH of the blood samples were performed at the pressure prevailing during the collection. A Cambridge Model R pH meter located outside the chamber was connected by suitable shielded cables to a glass electrode of the McInnes-Belcher type within the chamber. The electrode was enclosed in an electrically-shielded, plastic box through which a stream of dry air was circulated at ambient temperature. The apparatus was standardized before and after each determination by means of phosphate buffers of pH 7.00 and 7.38 at 25°C.; both of these were checked against buffers freshly prepared from U. S. Bureau of Standards phosphates and found to be accurate. The pH determinations were made anaerobically in triplicate upon samples which had been stored in salted ice water and were completed within 1 hour of collection of the blood at high pressure, within 4 hours at normal pressure. Measurements made at ambient temperature were converted to the corresponding values at 37°C. by the temperature coefficient of Rosenthal (44).

The carbon dioxide tensions of the blood samples were calculated from the observed carbon dioxide content, pH, hemoglobin content and oxygen saturation of whole blood by means of the Henderson-Hasselbalch equation, the carbon dioxide content of serum being estimated from that of whole blood by the nomogram of

TABLE 1. AVERAGE VALUES OBTAINED DURING INHALATION OF AIR AND O_2 AT 1 ATM. AND OF O_2 AT 3.5 ATM.

MEASUREMENT	GROUP I				GROUP II				GROUP III			
CEREBRAL	NO OF MEN	AIR 1 ATM	AIR 1 ATM	DIFF	NO OF MEN	AIR 1 ATM	O_2 1 ATM	DIFF	NO OF MEN	AIR 1 ATM	O_2 3.5 ATMS.	DIFF
Blood Flow (cc/100g/min)	8	56.	55.	-1.	8	55.	47.†	-8.	7	57.	43.*	-14.
Vascular Resistance (mm Hg/cc/100g/min)	8	1.3	1.4	+0.1	8	1.2	1.5	+0.3	7	1.1	1.7*	+0.6
O_2 Consumption (cc/100g/min)	8	3.5	3.6	+0.1	8	3.4	3.5	+0.1	7	3.3	3.5	+0.2
CO_2 Production (cc/100g/min)	8	3.4	3.5	+0.1	8	3.4	3.4†	0.0	7	3.2	3.6	+0.4
Respiratory Quotient	8	0.97	0.96	-0.01	8	1.02	0.97	-0.05	12	0.95	1.02‡	+0.07
ARTERIAL BLOOD												
O_2 Cont (vols %)	8	18.5	18.9	+0.4	8	19.0	21.0*	+2.0	12	18.7	26.0*‡	+7.3
CO_2 Cont (vols %)	8	50.5	49.5	-1.0	8	51.1	50.4	-0.7	12	50.0	46.9†‡	-3.1
pO_2 (mm Hg)	—	—	—	—	—	—	—	—	12	91	2100	+2000
pCO_2 (mm Hg)	8	40.	39.	-1.	8	40.	38.	-2.	12	39.	34.†‡	-5.
Hb Sat (%)	8	94.3	95.1	+0.8	8	96.3	100.0*	+3.7	12	96.1	100.0*	+3.9
pH	8	7.40	7.40	0.0	8	7.40	7.41	+0.01	12	7.40	7.43†‡	+0.03
INTERNAL JUGULAR BLOOD												
O_2 Cont (vols %)	8	12.1	12.2	+0.1	8	12.8	13.4	+0.6	12	12.6	17.8†‡	+5.2
CO_2 Cont (vols %)	8	56.7	55.9	-0.8	8	57.4	57.7†	+0.3	12	55.7	55.2‡	-0.5
pO_2 (mm Hg)	8	35.	35.	0.	8	37.	40.	+3.	12	38.	75.*‡	+37.
pCO_2 (mm Hg)	8	50.	48.	-2.	8	50.	51.*	+1.	12	50.	53.*‡	+3.
Hb Sat (%)	8	61.9	61.9	0.0	8	65.5	68.5	+3.0	12	65.2	89.3†‡	+24.1
pH	8	7.35	7.35	0.0	8	7.34	7.34	0.0	12	7.34	7.31*‡	-0.03
ARTERIOVENOUS DIFFERENCES												
A-V O_2 (vols %)	8	6.4	6.7	+0.3	8	6.2	7.6*	+1.4	12	6.1	8.1*	+2.0
A-V CO_2 (vols. %)	8	6.2	6.4	+0.2	8	6.3	7.3†	+1.0	12	5.7	8.3*	+2.6
A-V pO_2 (mm Hg)	—	—	—	—	—	—	—	—	12	53.	2000.*‡	+1900.
A-V pCO_2 (mm Hg)	8	10.	9.	-1.	8	10.	13.†	+3.	12	11.	19.*‡	+8.
A-V Hb Sat (%)	8	32.4	33.2	+0.8	8	30.8	31.5	+0.7	12	30.9	10.7*‡	-20.2
A-V pH	8	0.05	0.05	0.0	8	0.06	0.07*	+0.01	12	0.06	0.12*‡	+0.06
GENERAL												
Pulse Rate/min	8	70.	70.	0.	8	68.	61.	-7.	12	66.	58†	-8.
Respiratory Rate/min	8	15.	15.	0.	8	13.	15.	+2.	12	15.	16.	+1.
Mean Arterial BP (mm Hg)	8	79.7	82.3	+2.6	8	78.4	78.8†	+0.4	12	78.7	84.1‡	+5.4
Mean Internal Jugular BP (mm Hg)	8	10.7	10.7	0.0	8	9.8	8.9†	-0.9	12	10.0	8.2†	-1.8

* Indicates highly significant change ($P < 0.01$). † Indicates significant change ($P < 0.05$, > 0.01).

ONE STATISTICAL EVALUATION of the changes produced by O_2 at 1 and 3.5 atm. (*groups II* and *III*) was performed by comparison with the normal variations encountered in the subjects of *group I* during 1 hour of air breathing at normal atmospheric pressure. Symbols indicating significant differences from the results obtained in *group I* appear as superscripts. In a similar manner the effects of O_2 inhalation at 1 and 3.5 atm. were compared. Significant differences encountered in this analysis are indicated by the presence of symbols written as subscripts.

Van Slyke and Sendroy (45). Since for the sake of greater uniformity and accuracy it was desirable that all data should be referred to a body temperature of 37°C., a pK' of 6.105 and a Bunsen solubility coefficient (α) of 0.520 for carbon dioxide in blood were used as more representative of this temperature than the values employed to construct the standard 38°C. nomogram. In our hands the indirect procedure for

determining the carbon dioxide tension of blood gave a figure averaging 3 mm. Hg higher than that obtained on the same samples by our modification of the microtonometer method, which has no consistent error (46). The same discrepancy was also found to exist when the error of the indirect measurement was determined by analyzing whole blood and plasma samples of known gas tension prepared by macrotonometry. These findings agree qualitatively with those of Hickam and Frayzer (47) and appear to establish a significant systematic error of unknown origin in the indirect procedure. We therefore subtracted 3 mm. Hg from each of the values so obtained in the experiments to be described. This correction of course has no influ-

TABLE 2. EFFECTS OF O_2 INHALATION AT 3 TO 4 ATM. PRESSURE UPON CEREBRAL CIRCULATION AND METABOLISM

Subject	Inspired Oxygen Pressure		Cerebral											
			Blood Flow		Vascular Resistance		O_2 Consumption		CO_2 Production		RQ		A-VO_2	
	C*	E**	C	E	C	E	C	E	C	E	C	E	C	E
	atms.		cc/100g/min		mm.Hg / cc/100g/min		cc O_2/100g/min		cc CO_2/100g/min				vol. %	
R.P.D.	.2	4.0	59	44	1.3	1.8	4.2	4.1	3.7	4.1	0.87	1.01	7.1	9.3
R.P.K.	.2	4.0	53	—	1.4	—	3.7	—	2.8	—	0.77	1.01	6.9	7.8
R.H.M.	.2	4.0	43	—	1.7	—	3.7	—	3.6	—	0.98	1.18	8.6	6.2
R.E.A.	.2	3.5	57	—	1.3	—	5.0	—	4.8	—	0.97	0.85	8.7	7.1
A.E.Y.	.2	3.5	72	41	0.6	1.7	4.2	3.1	3.7	2.7	0.88	0.89	5.9	7.5
E.A.D.	.2	3.5	39	36	1.7	1.9	3.0	2.9	2.8	3.1	0.95	1.07	7.6	8.1
G.L.T.	.2	3.5	44	—	1.5	—	3.1	—	2.2	—	0.70	0.89	7.1	11.9
E.C.M.	.2	3.5	51	—	1.7	—	3.3	—	3.1	—	0.92	1.13	6.5	7.8
B.L.R.	.2	3.5	61	45	1.0	1.7	3.8	3.8	3.8	4.1	1.00	1.06	6.2	8.5
C.F.E.	.2	3.5	62	45	1.0	1.5	3.5	3.7	3.3	4.3	0.95	1.14	5.6	8.3
J.S.	.2	3.5	60	48	1.0	1.3	3.0	3.5	3.1	3.6	1.04	1.04	5.0	7.3
H.A.	.2	3.5	52	41	1.4	1.7	2.6	3.0	2.5	3.0	0.96	0.99	5.0	7.3
P.E.O.	.2	3.5	60	—	1.2	—	3.6	—	3.7	—	1.03	1.09	6.0	6.8
R.E.P.	.2	3.5	54	43	1.3	1.8	3.3	4.3	3.2	4.6	0.97	1.07	6.2	10.0
W.E.S.	.2	3.5	71	—	1.1	—	2.2	—	2.3	—	1.06	1.00	3.1	7.1
R.H.M.	.2	3.4	59	—	1.4	—	3.5	—	3.7	—	1.07	0.94	5.9	9.0
J.N.W.	.2	3.0	49	50	1.8	1.8	3.4	4.5	3.0	4.4	0.90	0.98	6.9	9.0

* *C* indicates control period of air breathing at 1 atm. ** *E* indicates experimental period of O_2 breathing at increased ambient pressure.

ence on the reported arteriovenous differences in pCO_2 or on the changes produced by oxygen inhalation.

Mean arterial blood pressure was determined with a damped mercury manometer and internal jugular venous blood pressure by a saline manometer attached through stopcocks to the vascular puncture needles used for blood sampling. In each instance the point of reference for blood pressure measurement was 10 cm. anterior to the skin of the back.

RESULTS

The averages and a statistical evaluation of our findings under the three different conditions described above are shown in table 1; individual measurements bear-

TABLE 3. EFFECTS OF O_2 INHALATION AT 3 TO 4 ATM. PRESSURE UPON ARTERIAL AND INTERNAL JUGULAR BLOOD GASES

Subject	Inspired Oxygen Pressure		O_2 Content				Dissolved O_2		Hb Saturation		O_2 Tension		CO_2 Content				CO_2 Tension				pH			
			Arterial		Int. Jugular		Arterial		Int. Jugular		Int. Jugular		Arterial		Int. Jugular		Arterial		Int. Jugular		Arterial		Int. Jugular	
	C*	E**	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E
	atm.		vol. %				vol. %		%		mm. Hg		vol. %				mm. Hg							
R.P.D.	.2	4.0	19.6	27.4	12.5	18.1	0.3	8.1	64.0	92.0	—	—	50.8	46.3	57.0	55.7	—	—	—	—	—	—	—	—
R.P.K.	.2	4.0	18.3	25.8	11.4	18.0	0.3	6.8	63.4	92.9	36	82	46.1	42.1	51.4	50.0	38	32	48	50	7.36	7.40	7.31	7.28
R.H.M.	.2	4.0	18.0	25.2	9.4	19.0	0.3	6.4	51.3	100.0	27	100	46.9	48.0	55.3	55.3	35	35	42	52	7.45	7.42	7.40	7.31
R.E.A.	.2	3.5	18.9	26.1	10.2	19.0	0.3	6.2	54.5	93.6	32	85	46.2	47.2	54.6	53.2	32	37	45	52	7.45	7.40	7.37	7.30
A.E.Y.	.2	3.5	18.2	25.5	12.3	18.0	0.3	6.5	64.2	89.7	35	79	51.8	50.7	57.0	57.4	39	38	50	55	7.41	7.42	7.34	7.31
E.A.D.	.2	3.5	19.3	25.6	11.7	17.5	0.3	6.6	61.0	90.8	35	72	52.6	50.1	59.8	58.8	40	36	53	58	7.41	7.43	7.34	7.29
G.L.T.	.2	3.5	16.5	23.9	9.4	12.0	0.3	6.4	56.9	67.6	36	41	52.1	45.7	57.1	56.3	43	33	53	56	7.36	7.42	7.30	7.28
E.G.M.	.2	3.5	18.0	24.8	11.5	17.0	0.3	6.0	62.1	88.7	37	70	49.5	45.4	55.5	54.2	43	36	53	60	7.35	7.39	7.30	7.24
B.L.R.	.2	3.5	19.1	26.5	12.9	18.0	0.3	6.6	64.6	88.5	38	66	48.6	45.5	54.8	54.5	38	33	52	53	7.40	7.43	7.31	7.30
C.P.E.	.2	3.5	18.6	25.7	13.0	17.4	0.3	7.2	69.3	89.1	40	64	49.1	44.0	54.4	53.5	38	29	48	46	7.40	7.47	7.34	7.35
J.S.	.2	3.5	18.7	25.7	13.7	18.4	0.3	6.6	73.2	96.0	42	97	50.2	47.4	55.4	55.0	38	32	47	49	7.41	7.46	7.36	7.34
H.A.	.2	3.5	18.2	25.7	13.2	18.4	0.3	5.6	65.1	89.7	36	67	48.2	46.0	53.0	53.2	37	32	45	50	7.40	7.45	7.36	7.32
P.E.Q.	.2	3.5	18.9	26.4	12.9	19.6	0.3	6.5	64.7	96.8	36	100	53.0	49.5	59.2	56.9	42	39	52	55	7.40	7.40	7.35	7.31
R.E.P.	.2	3.5	20.7	28.5	14.5	18.5	0.3	6.9	66.8	84.5	39	58	48.7	43.9	54.7	54.6	40	33	53	54	7.38	7.43	7.31	7.30
W.E.S.	.2	3.5	19.5	27.3	16.4	20.2	0.3	6.8	79.9	96.7	50	100	49.7	47.4	53.0	54.5	40	35	47	51	7.39	7.43	7.34	7.32
R.H.M.	.2	3.4	17.9	25.7	12.0	16.7	0.3	6.6	66.8	86.4	38	61	51.1	48.1	57.4	56.6	39	35	49	54	7.40	7.43	7.35	7.31
J.N.W.	.2	3.0	20.5	28.8	13.6	17.8	0.3	5.7	63.9	84.3	37	59	48.4	44.8	54.6	53.6	40	36	49	57	7.38	7.39	7.34	7.26

* *C* indicates control period of air breathing at 1 atm. ** *E* indicates experimental period of O_2 breathing at increased ambient pressure.

ing on the effects of the change from air breathing to inhalation of oxygen at pressures of 3.0 to 4.0 atm. are presented in tables 2, 3 and 4. The observations which appear to us to merit special attention are as follows.

Spontaneous Variations During Air Breathing at 1 Atm. No statistically significant changes occurred in any of the functions studied, indicating that considerable spontaneous variations in the composition of arterial and internal jugular blood, cerebral blood flow and cerebral metabolism are unlikely in healthy subjects under carefully controlled, resting conditions. Although no study of this type in normal

TABLE 4. EFFECTS OF O_2 INHALATION AT 3 TO 4 ATM. PRESSURE UPON RESPIRATORY RATE, PULSE RATE, BLOOD PRESSURE AND GENERAL BEHAVIOR OF SUBJECTS

Subjects	Inspired Oxygen Pressure		Resp. Rate		Pulse Rate		Blood Pressure				Signs and Symptoms
							Arterial		Int. Jugular		
	C*	E**	C	E	C	E	C	E	C	E	E
	atms.						mm. Hg				
R.P.D.	.2	4.0	7	12	63	59	79	86	6.0	4.8	PM
R.P.K.	.2	4.0	19	19	79	78	85	89	6.5	5.4	PSTC
R.H.M.	2	4.0	13	—	79	66	78	85	5.5	—	STM
R.E.A.	.2	3.5	20	12	75	51	87	91	10.0	9.6	PSTC
A.E.Y.	.2	3.5	13	11	58	56	59	82	11.3	10.0	O
E.A.D.	.2	3.5	13	13	57	57	77	78	8.6	8.4	O
G.L.T.	.2	3.5	11	10	49	48	77	79	9.6	7.9	P
E.C.M.	.2	3.5	12	11	53	49	97	108	9.4	7.9	O
B.L.R.	.2	3.5	15	20	79	71	78	88	17.2	10.2	O
C.F.E.	.2	3.5	17	32	71	62	72	76	8.0	6.7	T
J.S.	2	3.5	17	19	73	63	70	75	7.4	5.5	O
H.A.	.2	3.5	19	19	87	61	78	80	8.2	7.0	O
P.E.O.	.2	3.5	10	10	56	61	79	81	8.2	7.4	T
R.E.P.	.2	3.5	14	18	62	53	85	89	12.8	13.2	O
W.E.S.	.2	3.5	16	20	76	66	85	82	8.7	4.1	T
R.H.M.	.2	3.4	14	—	73	—	88	88	9.5	—	T
J.N.W.	.2	3.0	10	11	73	61	96	102	11.3	9.0	O

* *C* indicates control period of air breathing at 1 atm. ** *E* indicates experimental period of O_2 breathing at increased ambient pressure. Keys to signs and symptoms: P, pallor; M, mental confusion; S, sweating; T, twitching movements of a myoclonic nature; C, convulsions of generalized type; O, no discernible signs or symptoms.

men has been hitherto reported, Kety and his associates (48) obtained similar results in schizophrenic patients given small intravenous injections of amobarbital or Thiopental.

Effects of Oxygen Inhalation at 1 Atm. The changes produced by oxygen inhalation for 1 hour are in close agreement with those reported for shorter periods (30, 32, 49, 50) viz. a significant decrease in cerebral blood flow (15%) due to cerebral vasoconstriction with no change in cerebral oxygen consumption and a possible fall in arterial pCO_2 (2 mm. Hg) suggesting hyperventilation. A small but significant increase (1 mm. Hg) in the pCO_2 of internal jugular blood occurred. To our knowl-

edge the latter effect of oxygen inhalation at sea level has not previously been demonstrated to a statistically significant degree although the possibility of its occurrence has often been suggested (3, 21, 33, 51–55).

Effects of Inhalation of Oxygen at Increased Ambient Pressure. All of the changes encountered during oxygen inhalation at 1 atm. were observed here in intensified form but cerebral oxygen consumption remained unaffected. A more marked cerebral vasoconstriction decreased the rate of blood flow through the brain by 25 per cent. There was an unmistakable (5 mm. Hg) drop in arterial pCO_2 together with a greater (3 mm. Hg) rise in cerebral venous pCO_2. The oxygen saturation of internal jugular venous blood was about 90 per cent and the corresponding pO_2 was 75 mm. Hg. While both of these were considerably higher than during oxygen inhalation at 1 atm. the venous hemoglobin was far from completely saturated with oxygen as has been postulated should be the case. These findings indicate the simultaneous occurrence of cerebral vasoconstriction and hyperventilation, neither of which appears to have been taken into consideration in attempts at explaining the phenomena associated with oxygen inhalation at increased ambient pressure.

TABLE 5. EFFECTS OF O_2 INHALATION AT 3.5 ATM. UPON BLOOD O_2 AND CO_2 TRANSPORT (*Group III*, 12 SUBJECTS)

BLOOD MEASUREMENTS	1 Atm Air			3.5 Atm. Oxygen		
	Arterial	Internal Jugular	A-V Difference	Arterial	Internal Jugular	A-V Difference
O_2 Content (vols %)	18.7	12.6	6.1	26.0	17.8	8.2
Hb Sat (%)	96.1	65.2	30.9	100.0	89.3	10.7
pO_2 (mm. Hg)	91.0	38.0	53.0	2100.0	75.0	2025.0
CO_2 Content (vols %)	50.0	55.7	5.7	46.9	55.2	8.3
pH	7.40	7.34	0.06	7.43	7.31	0.12
pCO_2 (mm. Hg)	39.0	50.0	11.0	34.0	53.0	19.0

DISCUSSION

Our findings indicate that gross retention of carbon dioxide in brain tissue and intense constriction of the cerebral blood vessels can be excluded as important contributing causes of oxygen poisoning in man. A direct effect of oxygen on nerve cells remains the most likely explanation, but the diminution in oxygen uptake observed in *in vitro* studies could not be demonstrated in the human brain *in vivo*. Perhaps the most important finding of these experiments is that intrinsic adjustments of the cerebral vascular resistance with rising arterial pO_2 actually do comprise an important mechanism for reducing the mean pO_2 which the brain cells are exposed, as Dautrebande and Haldane (33) postulated. Since this 'protective' response to oxygen at increased ambient pressure appears to be intimately related to the observed disturbances in blood gas transport, respiration and cerebral circulation, it will be necessary to consider in some detail the interactions of these factors as seen in this study.

Blood Carbon Dioxide Transport. The effects of oxygen breathing at 3.5 atm. upon oxygen and carbon dioxide transport are most clearly demonstrated by the pertinent average data summarized for convenience in table 5. Due to the high arterial pO_2 the oxygen physically dissolved in arterial blood at 3.5 atm. was 6.5 volumes per cent (not tabulated), slightly in excess of the normal cerebral arterio-

venous oxygen difference of 6.1 volumes per cent during air breathing at 1 atm. If cerebral blood flow and oxygen consumption had remained unchanged this physically dissolved oxygen would have completely met the brain tissue oxygen requirements and the internal jugular venous blood would have contained no reduced hemoglobin. Actually the fall in cerebral blood flow during inhalation of oxygen at high ambient pressure resulted in an increased arteriovenous oxygen difference and the presence of 11 per cent of reduced hemoglobin in internal jugular venous blood. Nevertheless, this is only one-third the reduction of hemoglobin which occurred during air breathing at sea level, so that approximately two-thirds of the normally available carbon dioxide buffering capacity of hemoglobin could not be utilized during oxygen breathing at 3.5 atm.

The effects upon carbon dioxide transport of the diminished availability of base are shown in the lower half of table 5. When air was breathed at 1 atm. the pCO_2 of blood rose 11 mm. Hg on passing through the brain; at 3.5 atm. of oxygen it rose 19 mm. Hg. Of the 8 mm. Hg difference between these two figures it can be shown by the use of Henderson's nomogram (56) that approximately 5 mm. is due to the failure of hemoglobin reduction; the remaining 3 mm. must have been due to the observed decrease in cerebral blood flow. The changes of blood carbon dioxide content and pH from which the carbon dioxide tension was calculated confirm the relative inefficiency of the buffer mechanisms in blood during inhalation of oxygen at high pressure where, in spite of a lowered venous carbon dioxide content, pCO_2 rose and pH decreased.

The 3 mm. Hg average rise in internal jugular carbon dioxide tension at 3.5 atm. of oxygen and the increase in arteriovenous pCO_2 difference agree approximately with the determination by Behnke *et al.* (29) of a 6.5 mm. Hg increase in the pCO_2 of mixed venous blood of dogs breathing oxygen at 3.8 atm. In our subjects a further rise in internal jugular carbon dioxide tension was counteracted by a coincident fall of 5 mm. Hg in the arterial pCO_2, which in subsequent experiments was found to be the result of an increased alveolar ventilation. The absence of a similar decrease in arterial carbon dioxide tension in the experiments of Behnke *et al.* (5) may well have been due to the use of anesthetized dogs in which the sensitivity of the respiratory centers is diminished and in which the characteristic respiratory response to oxygen is depression, not stimulation (57).

Our measurements upon cerebral venous blood have revealed no sign of a rise of carbon dioxide tension to levels such as the 274, 368, and 246 mm. Hg observed, respectively, by Campbell (22), Seelkopf and Werz (25), and Taylor (24) who used the technique of subcutaneous or intraperitoneal equilibration of gas or fluid in rabbits and cats. Such tissue carbon dioxide tensions are approximately 100 times greater than those which have in our experiments been found due to failure of hemoglobin reduction. Pulmonary edema and prolonged apnea are known to be produced by high oxygen pressures in small animals (58–60) and the results of the equilibration techniques are more readily explainable by an interference with carbon dioxide elimination from the lungs rather than with its transport from the tissues. We have recently reported evidence substantiating this view (61).

Arterial and Internal Jugular Oxygen Tension. With the exception of the determinations of the oxygen content and tension in the arterial and mixed venous blood of anesthetized dogs made by Behnke and his co-workers (29), estimations of the exposure of tissues to high oxygen pressures appear to have been most often based upon the inspired oxygen tension and, occasionally, upon observations of the

color of venous blood (23). In the absence of measurements it has been generally assumed that on exposure to 3 or more atmospheres of inspired oxygen the cerebral venous hemoglobin saturation would be complete and the venous pO_2 very high. Evidence in favor of this assumption was presented by Bean (23) who found that external jugular blood withdrawn from anesthetized dogs breathing oxygen at 4 to 5 atm. was not only arterial in color but frothed in the sampling syringe which was located outside the pressure vessel.

In our experiments, however, cerebral venous blood withdrawn during oxygen breathing at 3 to 4 atm. did not froth on decompression. It could not be expected to do so because although arterial pO_2 averaged more than 2100 mm. Hg the sum of the partial gas tensions in the venous samples was much lower than 1 atm. More specifically, the observed slowing of cerebral blood flow actually brought about a drop of blood pO_2 of about 2000 mm. Hg and resulted in a pO_2 of only 75 mm. Hg in the internal jugular vein. This was only slightly higher than that found at sea level during air breathing (35–38 mm. Hg) or during oxygen inhalation (40 mm. Hg). We suspect that this disagreement with Bean's findings may in part be due to his use of external jugular blood, which normally has an oxygen content higher than that of the blood draining the brain, and to interference by anesthesia with cerebral vasomotor control (35).

Relationships of *in vivo* to *in vitro* Studies. In our subjects oxygen inhalation at 3.5 atm. produced no demonstrable alteration of cerebral oxygen consumption or cerebral respiratory quotient. This agrees with the findings of Stadie and Haugaard (17) and Dickens (9) that no change in oxygen utilization by rat brain tissue slices occurred until after an exposure to high oxygen pressure much longer than was required to induce severe intoxication in intact animals of the same species. Since several of our subjects showed objective signs of oxygen poisoning (table 4), it is clear that oxygen convulsions may occur in man even when the internal jugular pO_2 is less than 100 mm. Hg. How much of the brain tissue functions at a higher or lower pO_2 under these conditions can only be conjectured. Cells adjacent to the arterial end of a capillary are presumably exposed to nearly arterial tensions of oxygen but the rapid escape from the blood of oxygen carried in physical solution should result in a precipitous fall of the pO_2 within the cerebral capillaries. Thus the high rate of brain tissue metabolism and the relatively low diffusability of oxygen suggest that, even at several atmospheres of inspired oxygen pressure, much of the brain tissue mass exists at a pO_2 lower than that in the venous blood draining from it (62). It is conceivable that the early symptoms of oxygen intoxication, including convulsions, may originate from the noxious effects of very high oxygen tensions upon a rather small proportion of brain cells. These, in sufficient numbers, may act as trigger mechanisms to disturb the normal function of the larger mass of cells not necessarily exposed to toxic tensions of oxygen.

Barcroft (63) suggested that the mean oxygen tension in the tissue capillaries during air breathing at sea level could be roughly expressed as follows:

$$\text{Mean capillary } pO_2 = \text{venous } pO_2 + \frac{\text{arterial } pO_2 - \text{venous } pO_2}{3}$$

This empirical formula is not valid during oxygen breathing because of the presence of large amounts of oxygen physically dissolved in arterial blood. However, on applying to the data of table 5 the simple integration procedure by which Barcroft obtained his formula a value of about 850 mm. Hg is found for 'mean' cerebral capil-

lary pO_2 at 3.5 atm. of inspired oxygen. If such a gross approximation has any usefulness here it is to illustrate the likelihood that the major portion of brain tissue in *in vivo* experiments at 3.5 atm. probably is exposed to lower oxygen tensions than are thin slices or homogenates of brain tissue studied *in vitro* at 2 atm. of oxygen pressure.

Cerebral Circulation and Oxygen Toxicity. When very large amounts of oxygen are carried in physical solution by arterial blood a change in the rate of the cerebral circulation should constitute one of the most important factors determining the 'mean' cerebral capillary pO_2 (and possibly the latent period of oxygen toxicity). Inasmuch as the 25 per cent decrease in cerebral blood flow in our subjects at 3.5 atm. of oxygen pressure undoubtedly served to decrease the mean pO_2 in the brain, its cause becomes a matter of considerable importance.

It is evident from the 55 per cent average increase in cerebral vascular resistance that the reduced rate of blood flow was due to a cerebral vasoconstriction rather than to a fall in the mean blood pressure gradient (arterial minus internal jugular blood pressure), which was essentially unchanged. Cerebral vasoconstriction has been shown to occur in man at 1 atm. during oxygen inhalation (30, 32, 49) or hyperventilation (64), the latter producing the more marked effect. The question here is whether the vasoconstriction is to be regarded as the cause or the result of the hyperventilation. It could be the cause if, as Dautrebande and Haldane (33) suggested, the constrictor effect of the high pO_2 slowed the circulation through the cells of the respiratory center and caused an accumulation within them of acid products of their own metabolism. The concomitant 3-mm. Hg rise in cerebral venous pCO_2 fits well into this concept. This rise is about the same as that seen in man during inhalation of 2 to 4 per cent carbon dioxide in air at sea level, when, however, it is associated with a considerable increase in cerebral blood flow and decrease in cerebral vascular resistance (30, 31). Apparently the vasoconstrictor influence must have been exerted proximal to the capillaries and may have been limited or opposed by the concomitant rise in tissue pCO_2.

An alternative conception, not requiring the assumption of a direct constrictor action of oxygen, is that the primary mechanism is an interference with the buffer function of hemoglobin, necessitating the transport at a higher pCO_2 of the carbon dioxide produced in the respiratory center, thereby raising the pCO_2 within its cells. The resulting hyperventilation would lower arterial pCO_2 and thus bring about an increase in cerebral vascular tonus. From this viewpoint the slight retention of carbon dioxide produced by high oxygen pressures should be wholly advantageous.

Still other possibilities exist, including reflex respiratory stimulation due to irritation of the lungs (60, 65, 66) and an increase in the sensitivity of the respiratory centers (67) during exposure to oxygen at high partial pressures Either of these, by increasing alveolar ventilation, could lower arterial pCO_2 and contribute to a decrease in cerebral blood flow.

The evidence available to us does not permit positive evaluation of the relative importance of these and other potential causes of oxygen-induced cerebral vasoconstriction. It is noteworthy, however, that a 2000-mm. Hg increase in arterial pO_2 together with a 5-mm Hg fall in arterial pCO_2 produced no greater slowing in the rate of the cerebral circulation than the hyperventilation studies of Kety and Schmidt (64) indicate should be expected from the observed 5-mm. Hg fall in arterial pCO_2 alone. Similar results in subsequent experiments at different inspired oxygen tensions lead us to conclude that a physiologically important specific vasoconstrictor action

of oxygen probably does not exist in the intact human brain. We therefore prefer the other proposed explanations for the reduced cerebral blood flow during oxygen inhalation, which have in common a primary hyperventilation and an associated fall in arterial pCO_2. All are therefore in accord with the apparent causal relationship of the cerebral vasoconstriction to the lowered pCO_2 of arterial blood and with the findings of Bohr and Bean (68) that hyperventilation delays the onset of oxygen convulsions in cats.

Present Status of Role of Carbon Dioxide in Oxygen Toxicity. As noted above, the hypotheses that interference with carbon dioxide transport during exposure to very high oxygen tensions contributes to the central nervous system toxicity of oxygen by producing a severe carbon dioxide autointoxication (21) or by increasing the rate at which the blood carries oxygen to the brain (3) are invalidated by the results of our experiments in normal men. Furthermore, the importance of the rate of the cerebral circulation in determining the degree of exposure of brain tissue to high oxygen tensions suggests that the enhancement of oxygen toxicity by low concentrations of inspired carbon dioxide may only be the result of the well-known cerebral vasodilator effect of increased arterial pCO_2.

Our data actually support a different conception of the relationship of interference with carbon dioxide transport to oxygen intoxication. Regardless of the potential existence of other causes of the hyperpnea during exposure to high oxygen pressures, it is quite possible that a small increase in brain tissue pCO_2 played an important role in initiating and sustaining a sequence of interrelated events beginning with respiratory stimulation and followed in order by a lowering of arterial pCO_2, cerebral vasoconstriction, decrease in the rate of passage of blood through the brain and a fall in mean brain tissue oxygen tension. In direct contradistinction to Gesell's hypothesis the implication is that, aside from some as yet undemonstrated potentiation of oxygen toxicity by otherwise innocuous tensions of carbon dioxide, interference with carbon dioxide transport and its consequent slight retention in the brain may actually reduce the toxic effects of oxygen inhalation at several atmospheres pressure.

Summary

The effects of oxygen inhalation at 1 and 3 to 4 atm. ambient pressure upon blood oxygen and carbon dioxide transport, cerebral circulation and cerebral metabolism were studied in normal men. At 3.5 atm., oxygen inhalation produced a 55 per cent increase in cerebral vascular resistance resulting in a 25 per cent reduction in the rate of blood flow through the brain. Although these changes were approximately twice as great as those associated with oxygen inhalation at 1 atm. the differences were not statistically significant in this small series. The amount of oxygen physically dissolved in arterial blood at 3.5 atm. averaged 6.5 vol. per cent, or slightly greater than the normal cerebral arteriovenous oxygen difference during air breathing at 1 atm. Nevertheless, due to the slower rate of cerebral circulation, more oxygen was given up to brain tissue than was present in physical solution in the arterial blood. As a result the average internal jugular hemoglobin saturation at 3.5 atm. was 89 per cent. The removal of most of the physically dissolved oxygen produced a fall in pO_2 of about 2000 mm. Hg as blood passed through the brain. Partial interference with the normal reduction of oxyhemoglobin rendered less efficient the transport of carbon dioxide by the blood. Together with the diminished cerebral blood flow this accounted for an 8-mm. Hg increase in the arteriovenous

pCO_2 difference across the brain at 3.5 atm. of oxygen. Due to a 5-mm. Hg fall in arterial pCO_2 the elevation of internal jugular pCO_2 was limited to 3 mm. Hg. This is not compatible with the concept of a marked increase in brain tissue pCO_2 as a contributing cause of oxygen toxicity. No alteration in the rate of oxygen consumption or the respiratory quotient of the brain could be detected at 1 or 3.5 atm. of inspired oxygen.

The relationships of these findings to *in vivo* and *in vitro* studies of oxygen toxicity and to respiratory stimulation by oxygen are discussed. It is proposed that central accumulation of carbon dioxide on oxygen breathing at increased ambient pressures does not contribute to the toxicity of oxygen but rather may indirectly reduce the exposure of brain tissue to toxic levels of oxygen tension by producing hyperventilation and cerebral vasoconstriction.

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THE PATHOLOGICAL EFFECTS DUE TO INCREASE OF OXYGEN TENSION IN THE AIR BREATHED.

By J. LORRAIN SMITH, M.A., M.D.

(*From the Pathological Laboratory, Queen's College, Belfast.*)

THE investigation which forms the subject of the present paper arose out of a series of experiments on the attenuation of microbes by oxygen at high pressure. Part of this series was carried out with the view of ascertaining the effect of the oxygen on animals which had been infected. It soon became apparent, however, that the oxygen at a tension of over 100 % of an atmosphere produced pneumonia in the normal animal. It was therefore necessary to carry out a preliminary research in regard to this.

The literature of respiration records in connection with this question a considerable number of investigations, the most important of which were carried out by Lavoisier and others immediately after the promulgation of the combustion theory of respiration. According to various authors, definite effects were obtained by breathing pure oxygen. The respiratory exchange was increased, the circulation quickened, congestion of the lungs, or even inflammation and death, occurred. The theory was that addition of oxygen increased the pulmonary combustion, and thereby produced these pathological changes. This result was controverted by Regnault and Reiset in their classical investigation[1]. They showed that no increase in oxidation occurred and no pathological changes ensued on the exposure of animals to atmospheres rich in oxygen.

The question of the effect of oxygen took a new form in Paul Bert's research on the effects on animals of variations of barometric pressure. He discovered the fundamental law that the effects on all living organisms arising from variations in barometric pressure are entirely the result of the tensions at which the oxygen is maintained in the

[1] *Annales de Chimie*, p. 496. 1849.

various atmospheres. By exposing an animal to four atmospheres of oxygen, the same effect is brought about as that caused by increasing the barometric pressure of the air 20 times. In relation to the present investigation, the chief fact brought out is that oxygen at a tension varying from three to five atmospheres becomes toxic, and causes death in a definite form. The series of changes in the animal exposed to the oxygen, which Bert described, did not lead him to support the old combustion theory of respiration. He compares the symptoms with those of tetanus, or strychnine poisoning. The changes began with convulsions, and unless the tension were lowered in time, death of the animal ensued. In the experiments with small birds, he found that oxygen at a tension of 3½ atmospheres caused the onset of the convulsions after about 5 minutes' exposure. If the tension of oxygen were kept at this level, the convulsions continued to occur with decreasing severity, and at longer and longer intervals, till the animal died. If, however, the tension of oxygen were raised at the beginning distinctly beyond this, death ensued in the first attack. Another feature of this condition, of great pathological interest, was that the animal exposed to oxygen seemed to be thrown into a status epilepticus, and even if the high tension were replaced by that of ordinary air, the convulsions which had begun in toxic atmosphere, continued till death followed. The longest duration of this condition which Bert records, was in the case of a dog where the effect lasted for 24 hours after the dog had been removed from the high oxygen tension.

Bert directs attention to a farther point in regard to the fatal effect of oxygen on different classes of animals. While a tension of oxygen equal to 300% of an atmosphere produces convulsions in birds, a similar effect is not obtained in dogs till the tension rises to 380%[1]. He states, however, that he does not consider his experiments as sufficiently precise in regard to this aspect of the subject.

Bert regarded the effects as those of an agent toxic to the nervous system. The oxygen must cause these effects either by direct action, being carried in the blood to the nerve tissue, or by some indirect means, as, for example, by an effect on the blood itself. He carried out a number of transfusion experiments, in which he drew blood from an animal suffering from the toxic effects, and injected it into a normal animal. His negative results led him to conclude that the convulsions were due to the direct action of the oxygen on the nervous system.

[1] *La Pression Barométrique*, 794.

He then endeavoured, by means of blood-gas analyses, to discover the quantity of oxygen which must be present in the blood before the toxic effect arises. While he states that his analyses do not permit of a conclusion as to any constant value[1], the average obtained in the case of the dog was about 30 vol. per cent. Bert's conclusion accordingly was that oxygen at a certain tension (which can be most correctly stated as a tension of the gas in the air breathed) becomes a direct nerve poison, and that it is in this way that excess of oxygen kills an animal.

It would, however, seem *a priori* improbable that an excess of oxygen, which is harmful to the nerve elements, should be without effect on the other tissues of the body. Indeed Bert's observations on the diminution of respiratory oxidation when the tension of oxygen in the air breathed has risen beyond 100 % of an atmosphere, and the occurrence finally of complete arrest, clearly suggest that the lungs are affected by the oxygen. Further, since the question involves essentially a study of the action of oxygen on the tissues, it is clear that the lung is the most favourable organ for this purpose. In fact, we might say that Bert's investigation breaks down in this respect because he has to deal with the relation of oxygen to the nerve elements, and yet has no means of accurately determining the tension of the gas in this tissue. In the case of all tissues other than the lungs, we find in the circulating blood, which intervenes to carry the gas to them from the lungs, a factor whose effect on the tension of the gas we have no means of estimating.

The animals used in the present research were chiefly mice and small birds, although a few observations were made on rats, guinea-pigs, and pigeons. The advantage of using the smallest animals for these experiments is that the total amount of oxygen consumed is small, and therefore several hours must elapse before there is any appreciable fall in the oxygen tension of the atmosphere in a chamber even so small as the one now described. To obtain the effects due to moderately high oxygen tensions, each experiment had to be carried on for several days, and in such cases the smallest animals require the least attention.

The apparatus consisted of a pressure chamber to which was attached a mercury manometer 10 feet in height. The chamber was constructed out of strong brass tubing of 6 in. diameter, and 15 in. in length. The capacity was almost exactly 6 litres. To permit observa-

[1] *La Pression Barométrique*, 794.

tion of the animal during the experiment one end of the chamber was made of thick glass. This was fitted very carefully, and the fittings were covered with a layer of modeller's wax. The opposite end of the chamber could be detached, and was formed out of a disc of gun-metal $\frac{3}{8}$ inch in thickness. This disc rested on a strong collar, and between it and the collar was placed an india-rubber washer. To close it down tightly, a number of bolts were used, arranged round the circumference on a plan similar to that adopted in constructing the lid of an autoclave. The inner surface of the chamber was painted white. Two pieces of brass tubing were soldered into openings in the metallic disc, and by means of them a current of air or oxygen could be passed through the chamber after it was closed. The oxygen was obtained from cylinders supplied by the Scotch and Irish Oxygen Company. The gas was manufactured by the peroxide of barium method, and contained no impurity except nitrogen. The india-rubber tubing was that used for the manufacture of bicycle pumps. In the middle of the india-rubber, in this form of tubing, there is a strong layer of linen. This was found sufficient for the highest pressures. Tubing composed of ordinary india-rubber is very apt to give way at about 3 atmospheres' pressure.

An experiment was carried out in the following manner. There was placed in the chamber along with the animal a supply of food sufficient for two or three days, and enough sawdust and cotton-wool to keep the animal dry and warm. In the chamber there was also a gauze basket containing finely granular potash lime, to absorb the carbonic acid as it was excreted. After the chamber was closed, a current of oxygen was set going, and allowed to pass through the chamber until the air had been entirely replaced. About 18 litres were usually passed through in this way, the amount being measured by a meter. The outlet tube was then clamped, and the oxygen allowed to pass in till the pressure rose to the level determined on. As the oxygen became absorbed, the pressure was occasionally raised, and in the long experiments samples were taken at intervals for analysis. In those experiments where the oxygen was fatal, a post mortem examination of the animal was made, and the tissues examined microscopically.

The lowest tension of oxygen which has been studied is 40 % of an atmosphere. Above this, at intervals, experiments have been carried out till a tension of 450 % of an atmosphere was reached. The aim in this series was to find the effects which arise with tensions approaching by degrees that required to produce the toxic effect described by Bert.

Exp. I. Two mice were placed in the pressure chamber, and, without washing out the air, oxygen was passed in till the mercury showed a few inches positive pressure. Analyses of the gas in the chamber were made daily, and these gave an average tension of 41·6 % of an atmosphere. The mice were carefully observed; but as they showed no abnormal symptoms, at the end of 8 days the experiment was concluded. The temperature of the chamber was on an average 19° C., but varied from 17° C. to 22° C.

This should be regarded as a control experiment. It tested the method in several respects, but chiefly as to whether mice resembled man in their resistance to the effects of a very moderate oxygen tension. There is a large amount of experience on record in which men in caissons have carried on severe mechanical labour in this tension without any harmful result. Indeed, it is held by some engineers that so much oxygen increases the working power. This experience, however, does not exactly correspond to the experiments just recorded, since the exposure to oxygen in the caissons is intermittent, while in the experiment it is continuous, and if there were any effect, even of a minor description, the fact that it was continuous would relatively increase its severity. It was found, as will be pointed out later, that mice have a remarkable power of recovering from the effects of high tension oxygen. The same is probably true of man, so that in the alternation between the ordinary atmosphere and the atmospheres where oxygen is at an increased tension, there would be much less danger than in an exposure which is continuous. The absence of effect, however, shows that mice are, roughly speaking, not less resistant than man to oxygen.

In the next experiments, the tension of oxygen was raised to 70—80 % of an atmosphere.

Exp. II. Two mice were placed in the chamber, and the oxygen tension raised. The average of the daily analyses gave a tension of 73·6 % of an atmosphere. On the 4th day of the experiment, one mouse was found dead, and when examined showed congestion and consolidation of the lungs. The other mouse survived exposure for 8 days, and continued to live for 9 days subsequently in ordinary air, when it died from some accidental cause.

Exp. III. The experiment was repeated with the slightly higher oxygen tension of 79·9 % of an atmosphere. It gave the same result. One mouse died on the 4th day. In this case the congestion of the lungs was not so well marked as in the former case. The other mouse survived a week, when the experiment was concluded.

As experiments on the effect of oxygen these observations are not decisive, as the tension is not yet sufficiently high; but, in the light of the further results to be recorded, they may be regarded as indicating that at this tension a point has probably been reached where the oxygen has an effect on the lungs, which varies according to the resistance of the individual animal. The result is very similar to the observations in caissons, where it is found that one worker suffers while others endure the exposure without showing any effects.

It is convenient at this point to allude to some precautions which were found necessary in conducting the experiments. Special care was taken to avoid any fallacy from a fall in the body temperature of the mice. Most of the experiments were carried out in a small room which was maintained for the purpose at a temperature of from 17°—20° C., and in some the pressure chamber was kept warm by a gas flame. Another precaution taken was to provide for the absorption of the carbonic acid. The gauze basket with granular moist potash lime was found most effective. The amount usually present was ·05 %—·1 %, and was never higher than ·5%. The purity of the oxygen was also tested. Examination was made especially for the presence of ozone, or any other gas which might act as an irritant to the lungs. No impurity except nitrogen, however, could be detected.

It will also be noticed that in most of the experiments two animals were used. The purpose of this was to have a check on accidental circumstances in each experiment. It was found that the mice differed considerably in their power of resistance to the action of oxygen. A young mouse for example gives way more quickly than one that is fully grown.

In the experiments which follow next in the series, the tension of oxygen was about 130 % of an atmosphere. The effect on the mice was uniformly fatal, and the immediate cause of death was inflammation of the lungs. Embarrassment of respiration set in some time before death, and the lungs were found post mortem to be extremely congested, with more or less complete consolidation. Other changes were observed; for example, congestion of other viscera (liver, spleen, kidneys); but these were not of constant occurrence, nor were they so pronounced as the changes in the lungs.

Exp. IV. Two mice were placed in the chamber, and the pressure was raised to give a tension of oxygen of 128·6 % of an atmosphere. The mice were at first very active, and ran about the chamber in a very lively manner, as if stimulated by the oxygen. After 48 hours, they became sluggish, and

after 90 hours, they were found dead. The pressure was raised at frequent intervals to give an average oxygen tension of about 130 % of an atmosphere.

Post mortem examination: A. The lungs were deeply congested, and sank in the fixing fluid (saturated solution of corrosive sublimate). Spleen slightly enlarged. Other organs normal. On microscopic examination, the tissue of the lungs showed intense congestion in the large and small blood vessels. The alveoli were to a great extent filled with an exudate, which was granular and fibrillated in appearance, but did not give the fibrin stain by Weigert's method, nor with eosin. The Weigert's stain showed one or two streptococci. These, however, were exceedingly few in number, and as the mice died overnight in a somewhat warm atmosphere, their presence was probably accidental. There were no leucocytes in the exudate. The pneumonic condition was universal, and could therefore be compared only with the earliest stages of croupous pneumonia. The exudate itself was probably the cause of the embarrassed respiration and the animal's death. It is inconceivable that with inflammation so extensive, the animal could have survived until the process had developed farther. B. The lungs of the second mouse showed similar changes. There were no micro-organisms to be found in the sections. The liver and kidney showed congestion in this case.

In the post mortem records of cases in which death ensued from the effects of caisson disease, the occasional congestion of the viscera, including the lungs, liver, and spleen, has been noted. This is a suggestive detail in the observations, since it tends to show that the effects of high oxygen tension are not limited to the nervous system (Bert), nor to the lungs, but may affect other tissues as well. Pavy's experiments on glycosuria arising from passing oxygenated blood through the liver add confirmation to this hypothesis[1].

Exp. V. Two mice were placed in the chamber, and the oxygen tension raised to 128·9 % of an atmosphere. Mice became sluggish after 48 hours. Both died in about 69 hours. Post mortem examination showed the lungs congested and consolidated: other organs normal in both animals.

Exp. VI. Two mice were placed in the chamber, and the oxygen tension raised to 129·7 %. Both mice were found dead in 40 hours, and the post mortem appearances were similar to the previous experiments.

Exp. VII. Two mice were placed in the chamber, and the oxygen tension raised to 114 %. The mice died with consolidation of lungs after 60 hours' exposure.

[1] *Proceedings of the Royal Society*, 1875 and 1876.

The result is perfectly uniform. The oxygen causes a general pneumonia, which slowly developes to the stage at which the lungs are filled with a fluid exudation. Owing to this condition the animal dies. The average oxygen tension is 125·3 %, and the average time of survival is 64 hours. The regularity of the occurrence of pneumonia from oxygen at this tension lends further probability to the theory that workers in caissons at 4·25 % atmospheres air pressure, or a tension of 88 % of oxygen, are exposed to dangers from the effect of the oxygen on the lungs. It is further evident that the tension which, without exception, produces fatal results in mice is very slightly beyond this.

The next question to decide was whether raising the tension of oxygen distinctly above this point would give the same results at a markedly shorter period. Accordingly the pressure was raised so as to give an oxygen tension of 180 % of an atmosphere.

Exp. VIII. Two mice were placed in the chamber, and the oxygen tension raised to 182·9 % of an atmosphere. The mice were very lively at first, and ate their food greedily. In 23 hours one mouse was dead. The other died in 27½ hours. Post mortem examination: lungs deeply congested and consolidated. Spleen slightly enlarged in one of the mice. The other organs were normal.

Exp. IX. A small mouse, half-grown, and a full-grown mouse were placed in oxygen at a tension of 176·7 % of an atmosphere. In 10½ hours, the small mouse had embarrassed respiration, and was dead in 21 hours. The other mouse was at this time taken from the chamber, but died 3½ hours later. On post mortem examination, the changes in the lungs were found to be the same in character as before, but hardly so marked.

Exp. X. Two mice were placed in the chamber, and the oxygen raised to a tension of 188·5 % of an atmosphere. One of them died in 7 hours. The other was removed from the chamber and recovered.

Exp. XI. A guinea-pig was subjected to an oxygen tension of 166·5 % of an atmosphere. After 12½ hours, its breathing was very laboured, and it was drowned. The lungs showed marked congestion and œdema. This experiment was performed as a control on the foregoing experiments. The chamber was, however, inconveniently small for a guinea-pig. The oxygen absorption was so great that there was a rapid fall in pressure.

Exp. XII. A lark was placed in oxygen at a tension of 175·8 % of an atmosphere. After 11 hours the breathing had become exceedingly embarrassed, and the bird was taken out. It survived till next morning, but continued dyspnœic. Its arterial oxygen tension was observed by the carbonic oxide method, and was 10·7 % of an atmosphere. The arterial

oxygen tension of a normal bird is 35—40 % of an atmosphere. The lungs were markedly congested.

Exp. XIII. Two larks were placed in oxygen at a tension of 173·3 % of an atmosphere. One bird died after 16 hours, with congestion and consolidation of the lungs. The arterial oxygen tension of the surviving bird was 12·4 % of an atmosphere.

Exp. XIV. Two mice were placed in oxygen at a tension of 189 % of an atmosphere. Both mice died after 27 hours' exposure. The lungs showed the same lesions as in the other experiments.

In comparing these experiments with those in which the oxygen tension was 130 % of an atmosphere, the chief point of difference to be noted is that the time of exposure which mice and small birds can endure is not more than about 24 hours. The lesions produced by the oxygen are the same as those seen in the former series of experiments.

This lesion was also studied in regard to the modifications of function which it induces in the lungs. In a paper which I published in this *Journal* (Vol. XXII.) on the arterial oxygen tension in various pathological conditions, I recorded a series of experiments to show that exposure of animals to oxygen at a tension of 170—180 % of an atmosphere caused in a short time a diminution in the power of the lungs to actively absorb oxygen, and that with a continuance of this exposure the arterial oxygen tension fell till it reached the level for which mere diffusion of oxygen from the alveolar air might account. The inflammation now described is a further stage of the same process.

In concluding this set of experiments it seemed desirable to make an observation on the effect on mice of air pressure similar to the oxygen pressure. Two mice were exposed to air at the pressure of two atmospheres, for 48 hours, but showed no symptoms. The reason for making this observation is that Bert did not include observations on mice in his experiments on the comparison of the effects of air and oxygen pressure.

The experiments which have so far been recorded show that at a very moderate tension of oxygen the lungs become inflamed, and that the time of onset of the inflammation is earlier the higher the tension. Further, there is apparently no marked difference between mammals and birds in this respect. The inflammation developes slowly, taking about 24 hours when the tension is 180 % of an atmosphere, to reach a fatal stage. The pneumonia is therefore a much more slowly developing effect than the nervous symptoms described by Bert, and in regard to it there is not the same differentiation of the different

classes of animals. It should be noted, however, that, in contrasting the effect on the lungs with that on the nervous system, we have to bear in mind the fact that in mice and birds the alveolar oxygen tension is probably about the same, and therefore the lung cells in mouse and bird are exposed to the same tension of oxygen in any given atmosphere. Since, however, the absorbing power of the lungs differs in mice and birds, there is no reason to suppose that in a given atmosphere the nerve tissue of the two animals is exposed to the same oxygen tension. In fact, experiments are given later which indicate that these tensions normally differ very considerably. To further clear up this question a series of experiments were carried out to investigate the relation of the pneumonic to the nervous effect, and with this purpose higher oxygen tensions were now employed.

Exp. XV. Two mice were placed in the chamber, and the oxygen tension raised half an atmosphere beyond that of the former experiments, viz. to 230 %. In 9¾ hours both mice suffered from very marked dyspnœa, when the experiment was concluded. The mice recovered. This experiment illustrated the striking fact, observed throughout, of the remarkable power of recovery from this condition.

Exp. XVI. Two mice were subjected to oxygen at a tension of 285 % of an atmosphere. They were at first very lively. In 3¾ hours both were dyspnœic. After 8¾ hours, one died with congested lungs. The other recovered.

Exp. XVII. A rat was subjected to oxygen at a tension of 268 % of an atmosphere. The large absorption of oxygen by the rat introduced a certain amount of fallacy into this experiment. In 5 hours the respiration was very much embarrassed, and the animal died overnight.

Exp. XVIII. Two mice were subjected to oxygen at a tension of 300 % of an atmosphere for 1 hour 8 minutes. They showed during this time nothing abnormal. The tension was then raised to 354·9 %. After breathing this atmosphere for 1¼ hours, they showed dyspnœa: *i.e.* 2 hours 35 minutes after the experiment began. After 10¼ hours, they were taken out of the chamber, and they both died immediately thereafter. The lungs of both showed the characteristic pneumonia.

Exp. XIX. Two mice were exposed to oxygen at a tension of 357 % of an atmosphere. They were both dead after 5 hours, with the characteristic consolidation and congestion of the lungs.

There was no evidence of convulsive effects although the tensions were now as high as some of those used by Bert; but as I have already pointed out, it was with birds that the "*toxic effect*" was obtained at this tension.

Bert's experiment was therefore repeated in the following manner:

Exp. XX. Two larks were placed in the chamber, and the oxygen raised to a tension of 301·4 % of an atmosphere. They at once became excited, and moved rapidly about the chamber. After 13 minutes' exposure to this tension, they were simultaneously thrown into violent convulsions. These recurred at short intervals. They began to subside in about an hour. After 2 hours 7 minutes, the chamber was opened. One of the birds remained in an unconscious condition, with occasional epileptiform convulsions, for about 1 hour after, when it died. The other survived, and was very active and restless for a while, but became later very sluggish. When it was fed by the hand, however, it shook off its drowsiness for a short time, and again assumed its normal activity. It survived in this condition for several days. There was a remarkably small amount of dyspnœa. The oxygen seemed to abolish the fatigue which would arise after a similar effect in a normal bird. There was scarcely any hyperpnœa even. There was nothing noteworthy in the post mortem appearances.

This experiment fully confirms Bert's observations. The symptoms of toxic action were of the nature of strychnine effects. The effects, further, persisted in one of the birds after it had been restored to ordinary air. It occurred to me that the difference between mice and birds, which had hereby been clearly established, might be due to a difference in their respiratory function, rather than to a difference in the reaction of their nervous system. Before the oxygen can reach the nervous tissue, it must pass through the lung cells and the blood, and both these elements may have an effect in modifying the tension, which differs in the two cases[1].

A certain amount of evidence is already in our possession in regard to the differences in arterial oxygen tension which are due to the lung cells. In the paper just referred to, by Dr Haldane and myself, we have brought forward experiments on the oxygen tension of the blood as it leaves the lungs, which prove that the active power of absorbing oxygen possessed by the lungs of small birds is much greater than that of mice. In ordinary air small birds have an arterial oxygen tension of about 35—40 % of an atmosphere, while mice have an oxygen tension of 20—25 %. We farther showed that when the oxygen tension of the air breathed was increased to 80 % of an atmosphere, the same difference in absorptive power was still observed.

If then the onset of convulsive effects be in any way dependent

[1] This *Journal*, xxii. p. 231.

on the power of actively absorbing oxygen at a given tension, say 300 % of an atmosphere, it should be possible to abolish the effect by paralysing the functional activity. I have already referred to the experiments which have been published showing the manner in which this paralysis can be effected by exposing the bird to a moderately high tension for some hours[1]. This experiment was accordingly carried out as a preliminary to observing the effect of an oxygen tension of 300 % of an atmosphere.

EXP. XXI. Two birds were exposed to a tension of 140 % of an atmosphere. The tension, further, fell very considerably during the night. After 12 hours, the birds were taken from the chamber. They were quieter than normal, but showed no signs of difficulty in breathing. One of the birds was taken 2½ hours later, and was placed in oxygen at a tension of 300 % of an atmosphere. It remained in this atmosphere for 2 hours 38 minutes without showing the faintest tendency to convulsions. It showed dyspnœa after an exposure to the high tension of about 45 minutes. The experiment was concluded, and the bird was taken out. Its arterial oxygen tension in ordinary air was then observed, and found to be 16 % of an atmosphere, or less than 50 % of the normal. The lungs were markedly congested. The remaining bird was similarly examined 10 hours after it had been exposed to the oxygen at the moderate tension. It remained in oxygen at a tension of 300 % for 1 hour 15 minutes, and showed only dyspnœa. The arterial oxygen tension, observed next day, was 19 % of an atmosphere.

EXP. XXII. A control experiment was carried out at this stage, which consisted in exposing to oxygen at a tension of 300 % a normal bird and a bird whose lungs had been damaged previously by a moderate tension of oxygen. After 12 minutes the normal bird had convulsions while the other bird hopped about unconcernedly.

There are accordingly two phases of the oxygen effect. The one consisting in the slowly developing inflammatory effect seen most prominently in the lung tissue. The other a rapidly developing effect on the nervous tissue, which we may in the meantime describe as functional. In these experiments, we have seen oxygen at a tension of 300 % of an atmosphere giving rise to the inflammatory effect in mice in 5 hours. The same tension gave rise to the tetanic effect on the nervous system, in birds, in about 12 minutes. In what sense the two phases of oxygen effect resemble each other is obscure. Both effects persist after the animals have been restored to ordinary air, and this, since it is frequently inconsistent with recovery, we may regard as

[1] This *Journal*, XXII.

indicating a profound change in the tissue cells. It is also clear that the onset of the effect on the lungs acts as a protection from the nervous effects. It is probably in this way that the explanation may be arrived at of the subsidence of the nervous effect after some time.

A further experiment was made to ascertain if a tension of oxygen distinctly lower than 300 % could bring about convulsive effects.

Exp. XXIII. A bird was placed in the chamber and the pressure raised to 255 % of oxygen, at 11.23 a.m.

11.44 Suspicion of convulsions.
12.27 Restlessness, but no convulsions.
12.30 Pressure raised to 287 %—dyspnœa.
12.33½ Convulsions.
12.37 Experiment stopped.

From this experiment it is clear that below a tension of about 270 % of an atmosphere oxygen does not cause convulsive effects on birds.

It still remained to ascertain at what tension the nervous effects could be obtained in mice. Curiously enough, Bert, though he complains of the difficulty he experienced in obtaining oxygen in sufficient quantity for his experiments, did not make observations on mice. Hence there are on this point no data.

Exp. XXIV. A mouse was exposed to oxygen at a tension of 414 % of an atmosphere at 11.5 a.m.

11.20 No convulsions. Pressure raised to 450 %.
11.37 Mouse showed mild convulsions.
11.43 Convulsions more distinct.
11.55 Mouse removed from chamber. It was now sluggish in its movements.

Exp. XXV. The preceding experiment was repeated with two mice. They were exposed to a tension of 450 % of an atmosphere from the beginning of the experiment. One mouse died from the oxygen early in the exposure. The other showed convulsions after an exposure of 20 minutes.

The convulsions in neither of these experiments were so severe as those which were seen in the case of the birds.

These experiments again clearly exhibit the difference between mice and birds in respect of the nervous symptoms of oxygen poisoning, and we have seen that this difference can be to a certain extent abolished by damaging the lungs of the birds. The question which now presents itself is whether or not the bird with its arterial oxygen tension lowered

by damage to the lungs, would show the convulsive effects at the very high tension of 4·5 atmospheres of oxygen, at which they occur in mice.

Exp. XXVI. Two birds were exposed to oxygen at a tension of 166 % of an atmosphere for 10½ hours. They were then exposed to a tension of 308 % at 12.17 p.m.

12.47 Birds showed no sign of convulsions. Tension raised to 373 % of an atmosphere.

1.10 Birds still showed no signs of convulsions. Pressure raised to 450 % of an atmosphere. Convulsions set in at once.

1.30 Chamber opened. One bird was dead. The other was dyspnœic, and remained so for some hours afterwards.

The nervous effect therefore was only retarded by the paralysis of active absorption. The exact point at which the nervous effect returned would doubtless vary with the condition of the lungs. The following two experiments prove the same conclusion, though in a slightly different manner. If it be true that the onset of the lung effect is protective from the nervous effect, we should, in place of a preliminary exposure to a low tension, be able to raise the tension very gradually, by successive stages, until we reach the tension of 4·5 atmospheres before causing the convulsive effect. The experiments now recorded give the times of exposure at different stages, in order that this might be accomplished.

Exp. XXVII. A bird was exposed to oxygen at a tension of 239 % of an atmosphere at 1.45 p.m.

3.15 Tension raised to 252·9 %.

3.35 Bird became restless.

3.47 Tension raised to 271 %.

3.52 No convulsions.

4.15 Tension raised to 300 %.

4.38 Bird quiet. Dyspnœic. Tension raised to 324 %.

4.49 A few small spasms, but no convulsions.

5.3 Tension raised to 342 %.

5·7 Convulsions.

5.19 Experiment stopped.

Exp. XXVIII. A bird was placed in oxygen at a tension of 269·7 % of an atmosphere, at 12.40 p.m.

12.50 Restlessness. No convulsions.

1.10 Still restless, but no convulsions. Tension raised to 287 %.

1.12 Bird quieter. Slightly dyspnœic.

1.30 No convulsions. Tension raised to 303·4 %.
1.43 Convulsions, which subsided.
1.50 No trace of convulsions. Tension raised to 309·7 %. Small clonic spasms at once, which subsided.
2.5 No further development. Tension raised to 342 %. Bird now quiet. Dyspnœic.
2.10 Dyspnœa.
2.19 Dyspnœa increasing. Tension raised to 342 %.
2.25 Tension raised to 365 %. Bird quiet. Co-ordination difficult.
2.35 Tension raised to 408·9 %. Dyspnœa.
2.40 Convulsions. Apparatus burst.

In both these experiments the tension was carried distinctly beyond that which usually causes convulsions, and probably had the stages been taken more slowly it might have reached a still higher point.

Bert attempted, by means of direct observations on the quantity of oxygen which could be obtained from the blood of animals exposed to the high tension, to determine the conditions under which the tissues of the nervous system became poisoned. His hypothesis was that the saturation of the hæmoglobin of the blood was not complete till a very high tension had been reached, and that the tension which gave rise to convulsions corresponded with that at which not only was the hæmoglobin saturated, but the gas was beginning to pass into solution in the liquid part of the blood. The tissues, further, are supposed to be anaërobic, and the fatal effect was the result of the oxygen directly acting on the anaërobic elements[1].

Whilst this explanation of the dissociation of oxyhæmoglobin is incorrect, and the theory of the tissues also unsupported, it is important to remember that the "toxic" effect is due to tension, and not to quantity, of oxygen in the blood. It is possible to diminish the quantity of oxygen in the blood, and yet to bring about the convulsions at the oxygen tension of 300 % of an atmosphere, and the following experiment was carried out with this object.

Exp. XXIX. A bird was placed in the chamber, and beside it a bottle with a wide mouth inverted in a capsule containing water. In the bottle was a volume of carbonic oxide sufficient to give about ·4 % tension at a pressure of three atmospheres. When the oxygen tension had been sufficiently raised to make it safe to do so, the bottle was overturned, and the carbonic oxide gas allowed to escape into the chamber. When the oxygen

[1] *La Pression Barométrique*, p. 1154.

tension reached 300 % of an atmosphere, the convulsions set in as usual. At the end of this experiment, the blood of the bird was examined and the hæmoglobin was found to be 38 % saturated.

General Résumé.

It remains in conclusion to draw attention to the physiological and pathological investigations with which the one just recorded is in immediate connection.

It may be regarded in the first place as supplementary to the investigation on the normal process of respiration of oxygen, which has been carried out by Dr Haldane and myself. In that investigation we showed that the absorption of oxygen by the lungs is an active physiological process. The experiments just described show that at a tension a good deal higher than that of ordinary air, oxygen has the effect on the lungs of an irritant, and produces inflammation.

In the second place the experiments show that the toxic effects described by Bert occur at a tension which is much higher than that required to produce the inflammatory effect on the lungs. Further, it is shown that when the lungs are damaged the tension required for the production of this toxic effect is markedly higher than that required when the lungs are normal.

A subject on which these experiments have a direct bearing is the pathology of caisson disease. Since this subject requires separate investigation, I do not propose to discuss it fully at present. It is clear, however, that Bert in his experiments in regard to it, directed his attention chiefly to the effects of rapid decompression, to which he is inclined to ascribe the disease. Since workers in caissons are occasionally in 4·25 atmospheres of air pressure, they are undoubtedly within, at most, a very short distance of an atmosphere dangerous from the oxygen alone. Bert's investigations do not take into account the possible oxygen effects, and if we read the records of post mortem examinations of cases dying from caisson disease, not only is there a large amount of evidence regarding the congestion of the lungs and other viscera, similar to that produced in the mice in these experiments, but there is a scarcity of fatal accidents when caissons burst and decompression is instantaneous. Further, Bert admits that the only point on which all observers agree is that the risk of accidents to the workers is proportional to the time of exposure to the high pressure[1].

[1] *La Pression Barométrique*, p. 512.

It is unnecessary at present to adduce further evidence to show that the oxygen tension of the high pressure atmosphere is probably to be regarded as taking a part along with rapid decompression in the production of caisson disease. For investigation of this subject experiments must be conducted on lines differing from those now described.

Apart from the special interest of caisson disease, the experiments have a bearing on the general pathology of inflammation. The fact to which I would especially draw attention is that the inflammatory condition of the lungs is in a sense directly continuous with the normal process of respiration. The transition from the physiological to the pathological stage is imperceptible. Oxygen which at the tension of the atmosphere stimulates the lung cells to active absorption, at a higher tension acts as an irritant, or pathological stimulant, and produces inflammation.

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MEDICINE

UNDER THE CHARGE OF
JOHN H. MUSSER, M.D.
PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS, LA.

OXYGEN POISONING*

BY WILLIAM C. STADIE, M.D.
JOHN HERR MUSSER PROFESSOR OF RESEARCH MEDICINE

BENJAMIN C. RIGGS, M.D.
INSTRUCTOR

AND

NIELS HAUGAARD, A.B.
RESEARCH ASSISTANT

(From the John Herr Musser Department of Research Medicine,
University of Pennsylvania)

Introduction. Lavoisier had no sooner discovered oxygen and its significance to life than experimenters began to subject animals to concentrations of oxygen greater than that in the air. Indeed, Lavoisier himself with Seguin[118] established the fact, since abundantly confirmed, that inhalation of 1 atmosphere of oxygen does not alter the oxidative metabolism. Early, administration of oxygen to the sick made a strong appeal to the imagination—both lay and professional. Rational oxygen therapy slowly evolved and was put upon a sound basis by the introduction of the arterial puncture—to determine hemoglobin unsaturation, and the oxygen chamber, tent, and mask—to assure efficient administration. The improved technical production of cheap, pure oxygen was, of course, an important contributing factor in this advance.

Two other fields of human activity were meanwhile increasing, the one old, the other new: namely, deep-sea diving and flying. Oxygen inhalation at greater than normal pressures assumed importance in these. Paul Bert, devoting years to the study of physiologic reactions in the first of these fields, embodied his findings in his classic, *La Pression Barometrique* (1878).[40] For the first time he revealed that oxygen plays a dual rôle. On the one hand—at low pressures—it sustains life; on the other—at high pressures—it kills. "One finds clearly demonstrated," he said, "the apparently paradoxical result that under the influence of very high oxygenation

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of the blood, the tissues oxidize less, organic combustions diminish in energy, production of CO_2, excretion of urine, the destruction of sugar in the blood are diminished, and that as a result temperature falls." (Reviewers' translation.)

Thus began the subject of oxygen poisoning. Literature has accumulated; at first sight scanty, but upon search, surprisingly extensive. Various points of view were emphasized—deep-sea diving, aviation, microorganisms, new growths, enzymes, blood gas transport, therapy. Some wrote a paper or two; others devoted years to the subject. In his Harvey Lecture, Behnke[30] enumerated the fruits of these labors: Increased knowledge of alterations in the gaseous environment of man, increased efficiency of the diver and caisson worker, clarification of puzzling phenomena of flight, and greater possibility of salvage work on sunken wrecks.

There are three types of situations involving possible oxygen poisoning: (1) At high altitudes, as in flying, where supplemental oxygen is given to counteract the insufficiency of the air. Since the ambient pressure is low, there need be no excess oxygen pressure;* hence, as Armstrong stated,[12] "There have been no harmful effects from the use of oxygen in aviation except some of a relatively minor nature." (2) In deep-sea diving, in which toxic pressures of oxygen may be quickly reached. It is the dream of those interested that an understanding of the mechanism of oxygen poisoning will enable man to descend to depths limited by the strength of materials rather than his physiology. (3) In disease, particularly pulmonary and cardiac, producing insufficient saturation of blood hemoglobin, alleviated by oxygen administration. Poisoning may arise here if the safe dose is exceeded.

The first exposition of the subject was that of Bert. Subsequently Hill[95] devoted a portion of his book "Caisson Disease" to partial review and discussion of oxygen poisoning. Apparently there has been no exhaustive review. The authors present here a discussion of significant papers on the subject.

Bert, the discoverer of the phenomenon called it, according to the Hitchcock[40] translation, oxygen poisoning. By this is meant any variation from the normal structure or function attributable to the action of oxygen which produces deleterious effects.

Symptomatology. Excess oxygen produces characteristic symptoms and signs, the rapidity of onset and severity of which vary with the partial pressure of oxygen. While there seems to be general agreement that oxygen toxicity constitutes a clinical entity, there is less agreement on the incidence of specific symptoms, with the exception of those referable to the central nervous system.

1. *Nervous System.* Bert[40] studied the effects of increased air pressure on several animals, including birds, dogs and cold-blooded species. The outstanding symptom in all cases was convulsion, characterized by tetanus and opisthotonus, said to resemble strychnine poisoning. Later investigators described similar convulsions at various pressures in several species. Bornstein and Stroink[48] found clonic spasms developed in rats at 8 atmospheres of oxygen, Hill[96] and Shilling and Adams[152] described convulsions in several mammalian species at 2 to 5 atmospheres. Libbrecht and Massart[120] observed convulsions in mice at 4 atmospheres, and Hederer and Andre[91] found convulsions the presenting symptom in rabbits at from

* All pressures of oxygen will be stated in terms of atmospheres absolute. Ordinarily, when administering oxygen, it is sufficient to indicate the concentration by stating the per cent. At higher pressures, however, such a designation becomes confusing.

0.8 to 12 atmospheres of oxygen. Behnke *et al.*[36] subjected dogs to 4 atmospheres of oxygen for 2 to 4 hours, and found that 2 out of 9 developed convulsions, which were described as respiratory in type. Later, Shaw, Behnke and Messer[151] stated that "the symptoms of acute oxygen poisoning" (at 4 atmospheres of oxygen) "which are most apparent are the changes in blood pressure" (see below) "and the convulsive seizures of the head and neck." Although generalized convulsions have not been as frequently observed in man as in other species, Behnke stated[30] that "essentially oxygen induces transient idiopathic epilepsy in the apparently normal individual." More specifically, Bornstein and Stroink,[48] while finding no symptoms in man at rest for 45 minutes in 2 atmospheres of oxygen, observed clonic spasms of the legs with hyperactive patellar reflexes when the subject was working on a bicycle. Behnke, Johnson, Poppen and Motley[34] studied the effect upon man of 1 to 4 atmospheres of oxygen, and described the symptoms as all referable to the nervous system; these included more or less generalized convulsions, syncope, and loss of coördination and attention. Thomson[164] observed 2 naval officers under 4 atmospheres of oxygen; 1 of these developed facial twitches in 16 minutes and the other, a tremor of the lips. When the second subject was returned to air at normal pressure, clonic seizures were followed by unconsciousness. The possibility that the symptoms in the second case were due to aëro-embolism cannot be excluded. (See section on Aëro-embolism.) Behnke, Forbes and Motley[33] studied the effects of oxygen at 4 atmospheres on men. They measured visual changes to be described later, but also observed dizziness, stupefaction and a "sense of impending collapse." Substitution of air by removal of the mask was followed by recovery and a sense of exhilaration. Becker-Freysang and Clamann[27] subjected themselves to 0.9 atmosphere of oxygen for 60 hours, and after the first 24 noticed paresthesias of the fingers. Behnke[28] described true epileptiform convulsions developing 45 minutes after subjection to 4 atmospheres of oxygen. In a review of observations pertinent to submarine salvage work, Jenkinson[109] gave as characteristic symptoms twitching of the head and neck, convulsions and paresthesias. Moody and Howard[132] described convulsions in a child with pneumonia who was treated for 6 days in an oxygen tent with a concentration presumed to be over 0.7 atmosphere although it was not measured in this case.

The non-specificity, or general nature of the central nervous system response to high oxygen is suggested by the observations of Bean and Rottschafer[25] that the removal of the cortex, and even of the cerebrum in dogs had no appreciable effect upon the convulsions produced by 5 to 6 atmospheres of oxygen.

There has been only one piece of work done on the special senses, by Behnke, Forbes and Motley,[33] who found that 3 atmospheres of oxygen produced, among other effects, a reversible loss of visual acuity, contraction of the fields to the tubular type (reminiscent to the Reviewers, of that seen in advanced central nervous system lues) but with pupillary dilatation.

The mental effects of oxygen at high pressures were first described in detail by Hill and Phillips.[101] They associated personality types with the appearance of certain symptoms. For example, those divers showing overcontrol, suppressed fears and resentment of observation and direction, designated by the authors as the "philosophical type," were prone to show work failures, dizziness and claustrophobia at 7 to 8 atmospheres of air pressure (oxygen = 1.4 to 1.6 atmospheres). In contrast, the

"practical type" were relatively free of symptoms. Nitrogen narcosis as a contributing factor in these symptoms was not discussed by the authors. Previous to this, Binger and Faulkner[42] had found that rabbits and dogs became drowsy within 3 days, breathing 0.8 atmospheres of oxygen, although Paine, Lynn and Keys[137] later produced lethargy in dogs in 2 hours at 1 atmosphere of oxygen. Davidson,[77] working with 1 atmosphere of oxygen, found no effect upon reaction time in choice tests in 20 minutes, but Shilling and Willgrube,[154] in a highly quantitative report, showed a slowing in problem-solution, cross-out tests and light-to-touch reactions with increasing pressure. The amount of slowing was also related to the subject's mental ability. To eliminate possible confusion with nitrogen narcosis, they studied these effects with increasing time at a given pressure and with increasing experience, and found the mental slowing was reduced in each case. Haldane[90] distinguished the mental effects of high oxygen from those of high carbon dioxide and nitrogen in the period of recovery: in the former, there is marked terror, but in the latter two, there is calmness. Behnke[30] described "mental torpidity" as characteristic of oxygen poisoning. Although the effects of oxygen on the respiratory system will be separately considered, it should be mentioned here that Barach[15] found, in patients with a preëxisting chronic anoxia, that inhalation of 0.5 atmosphere of oxygen produced profound but reversible disturbances in mental functioning, consisting of deep sleep and stupor followed by coma and delirium. This finding supports Hill's statements[95] that coma and paralysis are frequent symptoms in animals.

Respiratory Symptoms. As the discussion on the disorders produced by high oxygen will demonstrate, the respiratory system is second only to the nervous system in its apparent susceptibility to the gas. The first symptom to be expected is dyspnea. While Hill[95] pointed out that the earlier authors, from the time of Lavoisier to 1912, described respiration under increased air pressure as variously increased and decreased in amplitude and frequency, there seems to have been little mention of dyspnea. Hill found this symptom dominant in several species of warm-blooded animals, and earlier in onset than the central nervous system symptoms. Binger, Faulkner and Moore[42] found that dyspnea and cyanosis were the dominant symptoms in rabbits and dogs exposed to 0.8 atmosphere of oxygen for longer than 3 days. (This is related to the pulmonary changes to be described later.) Most of the rats placed in 1 atmosphere of oxygen for 3 to 4 days by Boycott and Oakley[49] showed increasing dyspnea as the only symptom, and died apparently from dyspnea described as "explosive." Paine, Lynn and Keys[137] also found dyspnea the most important symptom in dogs placed in 0.9 to 1 atmosphere of oxygen; the time of development varied from 4 to 75 hours. Gesell[88] found essentially the same symptoms.

Passing from dyspnea to more general variations in respiratory effort, Achard and Leblanc[2] described the death of guinea pigs and rabbits in 0.8 atmosphere of oxygen as due to asphyxia following slowed and jerky respiration appearing in the second day. Smith, Heim, Thomson and Drinker[158] subjected rats to 4 atmospheres of air pressure (0.8 atmosphere of oxygen), and noted that on the 3rd day, the animals were acutely ill, showing hyperpnea and cyanosis. In connection with the convulsive seizures described by Shaw, Behnke and Messer above,[151] these authors further stated that the seizures are "essentially inspiratory convulsions and are not unlike those in certain types of asphyxia." The convulsive period was, in fact, "terminated by respiratory failure." Behnke[28] found

in healthy males after a 7-hour "tolerance period" in 1 atmosphere of oxygen, an increased respiratory depth. Finally, Paine, Keys and Lynn[137] described the death of dogs in 0.9 to 1 atmosphere of oxygen within 48 to 120 hours as occurring after a period of respiratory distress. Marshall and Rosenfeld[126] found in addition that the administration of oxygen will enhance the respiratory depression from various drugs to the point of apnea and respiratory failure. Although more important from a metabolic point of view, the measurement of respiratory minute volume also bears a relationship to respiratory symptoms. While Hill[95] could find little change under compressed air, Clark-Kennedy and Owen[72] reported a decrease in pulmonary ventilation when the oxygen was raised to only 0.26 atmosphere (far below the minimum concentration at which most authors report symptoms). On the other hand, Bean,[17,18] found an increased respiratory minute volume in dogs at 4 to 5 atmospheres of oxygen, and Bean and Haldi[24] confirmed this in dogs at 5 atmospheres, although there was no increase at 1 atmosphere. Bean and Rottschafer[25] also found an increase at 5 to 6 atmospheres in decorticate and decerebrate dogs. In man, however, Behnke, Johnson, Poppen and Motley[34] found no change in minute volume at pressures from 1 to 4 atmospheres. In fact, "the irritative effect of oxygen on the lungs was noted in only one subject" (out of 10) "on a single occasion," although an increase in respiratory rate was observed. The single occasion was at low pressure (1 atmosphere). Schwab, Fine and Mixter[148] found no change in respiration in patients breathing 1 atmosphere of oxygen for 3 hours. Similarly, Becker-Freysang and Clamann[27] could detect no consistent change in respiration in themselves at 0.9 atmosphere of oxygen for 60 hours, although at the end of the experiment one of the authors developed bronchopneumonia, presumably a result of the high oxygen tension. Vital capacity was decreased in 1 subject and unchanged in the other. In dogs subjected to 1 atmosphere of oxygen for 6 minutes, Watt, Dumke and Comroe[168] found a transient diminution in respiratory minute volume of 11 to 13%. After elimination of respiratory chemoreceptors by the denervation of the carotid and aortic bodies, however, there was no change, and sometimes an increase. The authors concluded that since the chemoreceptors are continuously activated by the usual degree of oxygen unsaturation of the blood, the decrease of this saturation by high concentrations of oxygen eliminates this activation, resulting in diminution in respiratory minute volume.

Two general conclusions seem warranted from the evidence given above. The first is that respiratory symptoms are dominant in the action of oxygen at 0.8 to 2 atmospheres, while central nervous system symptoms are dominant above this level. This may perhaps be because at high pressures, death due to central nervous system symptoms precedes the possible development of pulmonary symptoms. The second conclusion is that in any case oxygen appears to be less irritating to the pulmonary system in man than in other species. However, conclusions with respect to man must be guarded since data are limited.

Cardiovascular Symptoms. Because of the comparative paucity of data, it is convenient to group together the heart rate in the intact organism, the blood pressure and the vasomotor signs of pallor and flushing. Bert observed[40] that under 3 to 4 atmospheres of air pressure (oxygen = 0.6 to 0.8 atmosphere), the pulse rate was lowered, and there appeared to be an increase in arterial tension, although this was not measured. Hill[95] confirmed the results obtained by other early investigators who found no

appreciable change in either pulse rate or blood pressure. Parkinson[138] observed a definite decrease in pulse rate when men breathed oxygen through masks at atmospheric pressure for 30 minutes. A similar observation by Dautrebande and Haldane[76] with an increase in the bradycardia as the pressure was raised to 2 atmospheres was explained by these authors as a possible protective mechanism against excessive changes in respiratory metabolism. Bean found a definite decrease in pulse rate in dogs subjected to 4 to 5 atmospheres of oxygen[17,18] which he compared to a similar result from the administration of carbon dioxide. Richards and Barach[143] kept 2 normal subjects in 0.5 atmosphere of oxygen for 7 days, and while there was no appreciable change in cardiac output, they noticed a fall in pulse rate. Shaw, Behnke and Messer[151] concluded from their experiments on dogs that the first sign of oxygen poisoning was a fall in blood pressure, a point which was disputed by Bean and Rottschafer[25] who found that the blood pressure change was not consistent in dogs at 5 or 6 atmospheres. They also found that the bradycardia was dependent upon an intact vagus, a point later substantiated by Bean and Whitehorn.[26] On the other hand, when observing men in 3 and 4 atmospheres of oxygen, Behnke, Forbes and Motley[33] noticed that a rise in blood pressure accompanied the other signs of poisoning, which included pallor and an increase in pulse rate. Becker-Freysang and Clamann,[27] after 24 hours in 0.9 atmosphere of oxygen, found no marked change in their pulses, with the exception of an attack of paroxysmal tachycardia (which is not necessarily related to the oxygen); they made no measurements of blood pressure. Schwab, Fine and Mixter[148] observed a bradycardia of 60 for the first $\frac{1}{2}$ to 1 hour in patients breathing 1 atmosphere of oxygen; there was no change in blood pressure or color in 3 hours. However, at 7 hours in 1 atmosphere, Behnke[28] found that healthy males showed a rise in pulse rate accompanied by pallor, which was replaced by flushing as the time was extended. This was explained as a possible sympathetic stimulation followed by parasympathetic, suggesting the action of a histamine-like substance.

In connection with this, Willmon and Behnke[170] found 1 man who when exposed repeatedly to 2.5 atmospheres of oxygen, developed an allergic response, characterized by dermatitis and generalized wheals which were relieved by a preparation of histaminase. However, no similar cases have been found in the literature.

Several less clearly defined symptoms of oxygen poisoning are described in man and animals. Malaise is described by Becker-Freysang and Clamann,[27] perhaps due to the concomitant development of pneumonia; anorexia is described by Binger, Faulkner and Moore,[42] Boycott and Oakley,[49] and Paine, Lynn and Keys;[137] nausea and vomiting were observed by Becker-Freysang and Clamann[27] and Behnke[28] who also found several subjects under oxygen at 1 atmosphere who complained of substernal distress.

Summarizing the cardiovascular changes, although there is not complete unanimity, the bulk of evidence shows that high tensions of oxygen are usually accompanied by a bradycardia which is apparently of vagal origin. As to blood pressure variations, there is neither sufficient agreement nor evidence to warrant a conclusion. Similarly, the observations are too few and scattered to allow a generalization about other symptoms, which appear to vary considerably.

Pathologic Anatomy. Since a review of the symptomatology seems to warrant the conclusion that at tensions of oxygen up to 2 atmospheres, the damage is chiefly pulmonary, and at higher pressures it is chiefly upon the central nervous system, one looks first for lesions in these 2 systems.

Noting that oxygen at a greater concentration than 0.6 atmosphere is toxic, Armstrong[11] stated, "The pathology in these cases indicates that the toxic action is restricted to the respiratory tract with congestion, edema, pneumonia and death occurring in that order." Behnke[28] stated that pure oxygen is a pulmonary irritant. Shilling and Adams[152] concluded, "the convulsions and pulmonary damage are separate, unrelated phenomena, both caused by the high tension of oxygen but acting in different manners." Unfortunately, there have been no exhaustive studies made of nervous system lesions following oxygen poisoning, and there is no evidence that any occurs. In fact, with the exception of non-specific changes in a few other organs to be mentioned later, pathologic changes appear to be limited to the lungs. Hill[95] credits L. Smith with the discovery that a slow increase of oxygen pressure causes congestion of the lungs, with the result that there is no "quick rise in oxygen tension in the blood, and so the convulsions fail to appear." Hill describes edema and exudate as the chief features of lung pathology. The first detailed studies, however, were made by Karsner[112] and by Karsner and Ash[113] of both gross and microscopic changes following exposure to oxygen at 0.8 to 1 atmosphere. The lungs of rabbits so treated showed congestion, edema, epithelial degeneration and desquamation, fibrin formation and finally pneumonia, as the time of exposure increased to 48 hours, and as the concentration of oxygen was raised from 0.5 to 1 atmosphere. Smith, Bennett, Heim, Thomson and Drinker[157] carried out a similar study with rats exposed to 4 atmospheres of air pressure (equivalent to 0.8 atmosphere of oxygen). They found progressive cellular hypertrophy and hyperplasia of the alveoli which persisted for months after return to normal pressure. These changes occurred in both young and old rats, but to a greater extent in the older ones. The final histologic structure resembled an exaggeration of that normally found in unexposed young rats. The younger animals and those that had been previously exposed showed an increased tolerance or adaptation to high pressures. The possible protective function of these structural changes was suggested by further investigation along the same lines by Smith, Heim, Thomson and Drinker,[158] who also found thickening and hyalinization of the walls of pulmonary arterioles and large arteries, with occasional thrombosis. The vessels were said to resemble those seen in chronic nephritis. Hederer and Andre[91] also found greater tolerance to oxygen in young than in older rabbits; however, rather than an increased tolerance with previous exposure, they found increased sensitivity. A similar sensitization was found by de Almeida.[78] Behnke *et al.*[36] demonstrated pulmonary pathology in part of a series of dogs exposed to 4 atmospheres of oxygen, but found the onset of convulsions the same as in those without such changes. The basic pulmonary changes consisting of edema, exudation and congestion were all reported in various species by Bornstein and Stroink,[48] Achard, Binet and Leblanc,[1] Achard, Leblanc and Binet,[2] Binger, Faulkner and Moore,[42] Pflesser,[140] Armstrong,[11] Orzechowski and Holzknecht,[135] Binet, Bochet and Bryskier,[41] Paine, Keys and Lynn,[136] and Paine, Lynn and Keys.[137] In addition, true hemorrhagic extravasation was observed in turtles exposed to 0.9 atmosphere of oxygen by Faulkner and Binger.[82] Other pulmonary signs of oxygen poisoning include massive pleural effusion, seen in rats exposed to 1 atmosphere by Boycott and Oakley,[49] pulmonary hemorrhage in several mammalians, seen by Shilling and Adams[152] in pressures as high as 4 atmospheres of oxygen, and atelectasis at 4 atmospheres, found in dogs by Behnke *et al.*[36] The literature contains no reports of pathologic studies

of the lungs of man dying from the effects of high oxygen pressure, but there is some indirect evidence. When Becker-Freysang and Clamann[27] exposed themselves to 0.9 atmosphere of oxygen for 60 hours, one of them developed all the signs of bronchopneumonia at the end of the experiment, and required 10 days to recover. Jenkinson[109] drew upon his experience in submarine salvage work to state that high concentrations of oxygen at atmospheric pressure administered for several hours may bring on consolidation.

There is no evidence in the literature of lesions in the central nervous system.

There is a scattering of observations on the lesions in other organs following exposure to high oxygen tensions. Achard, Leblanc and Binet[2] described congestion in abdominal viscera, de Almeida[78] found atrophy of the testicles in rats, and Paine *et al.*[136,137] observed intense contraction of the spleen and distention of the stomach.

In conclusion, with the exception of minor effects upon abdominal viscera, the morphological changes caused by high pressures of oxygen are apparently limited to the lungs and pulmonary vessels.

Blood. 1. *Formed Elements and Hemoglobin.* Surprisingly, the first record found in the literature of a quantitative report on hemoglobin and red cell changes in the circulating blood under the influence of increased oxygen tensions was that of Campbell in 1926,[59] who observed a decrease of both in rabbits breathing 0.5 atmosphere of oxygen for 5 weeks; this change he considered a part of acclimatization. In contrast, Achard, Leblanc and Binet[2] found, in short exposures (0.8 atmosphere for 2 days), a marked increase of both red and white cells in rabbits and guinea pigs. In later papers, Campbell[66] reports a decrease in hemoglobin and red cells in several species of mammals in oxygen at about 1 atmosphere, and in rats at 6 atmospheres.[57] Izumiyami[108] likewise found a diminution in hemoglobin and red cells in 7 human subjects breathing 1 atmosphere of oxygen.

Boycott and Oakley,[49] in order to determine marrow activity, estimated the reticulocytes as well as the hemoglobin concentration in rats in 0.5 and 0.65 atmosphere of oxygen for 2 months. While there was some diminution in the hemoglobin concentration at 65% atmosphere, they concluded from the reticulocyte counts that, if anything, marrow activity was merely slowed down. Anthony,[9] and Anthony and Beudenkopf[10] made extensive measurements of human red cells and hemoglobin while the subjects were breathing oxygen through masks for 20 minutes and found an average drop in number of red cells of 7.8% and in hemoglobin of 3.3% with a corresponding increase in the color index. While breathing 0.9 atmosphere of oxygen, Becker-Freysang and Clamann[27] found a slight increase in red cells, and Paine, Keys and Lynn[136] showed a rise in hemoglobin concentration in dogs breathing 1 atmosphere. Similarly, Binet, Bochet and Bryskier[41] found, after an initial fall, a marked rise in red cells of guinea pigs, mice and pigeons in 0.7 to 1 atmosphere of oxygen.

The possibility that high pressures of oxygen alter blood hemoglobin apparently has not been investigated. Brooks,[52] however, reports a study on the relation of the rate of oxidation of hemoglobin and the partial pressure of oxygen. In the presence of certain oxidizing agents the rate is maximum to an oxygen pressure of 22 mm. The significance of this to oxygen poisoning is unknown.

Summarizing the changes in blood cells and hemoglobin, while the majority of observers with the most extensive data report a decrease in

red cells and hemoglobin, a minority report the opposite. Symptoms of pulmonary irritation or variations in the concentrations of oxygen studied do not give a consistent explanation for the difference. There are only 3 reports in the literature of determinations of white cells. Achard, Leblanc and Binet[2] found them to be increased in guinea pigs and rabbits breathing 0.8 atmosphere of oxygen, and 1 of 2 human subjects studied by Becker-Freysang and Clamann[27] showed slight leukocytosis in 0.9 atmosphere. Behnke, Johnson, Poppen and Motley[34] found a slight leukocytosis without change in the differential from 2 hours exposure to 3 atmospheres of oxygen.

2. *Blood Chemistry.* Shilling, Thomson, Behnke, Shaw and Messer[153] determined a great many chemical blood and urinary constituents in animals exposed to high oxygen pressure, but found appreciable changes only in inorganic phosphate and sugar in the blood, which decreased. The drop in blood sugar sonfirmed a similar finding by Izumiyami[108] in man and animals. They also found a decrease in chlorides, serum albumin and viscosity, which returned rapidly to normal after removal from the oxygen. Although Shilling *et al.*[153] found no great change in non-protein nitrogen, Binet, Bochet and Bryskier[41] found a rise in blood urea and uric acid in mice, guinea pigs and pigeons, and Paine, Lynn and Keys[137] found a 6 mg. per 100 cc. rise in non-protein nitrogen in dogs. Campbell[63] reports a significant increase in blood histamine in rats following exposure to 5 atmospheres of oxygen (0.5 to 1.3 gamma per cc.), the meaning of which is not apparent since he also found that injection of histamine had no effect on oxygen poisoning. This may be related, however, to Willmon and Behnke's finding[170] of an allergic response to oxygen in a man, relieved by histaminase (see section on Symptoms).

The finding of an increase in blood lactic acid by Bean and Haldi[24] in dogs subjected to oxygen pressures up to 5 atmospheres is a solitary observation of uncertain meaning.

Summarizing the changes in the blood, high oxygen pressures seem to produce a small but significant decrease in red cells and hemoglobin, and a slight leukocytosis. Various minor changes in blood chemistry occur, including an increase in histamine, but the significance of these is not clear.

The Circulation and Peripheral Vessels. Little work has been done on the actual measurement of cardiac output and blood flow, and the few observations recorded are limited to the vessels of the brain and retina. Pulse rate and blood pressure apparently tend to be lowered, although there is little consistency in the literature (see the section on Symptoms). Hill[95] confirmed a number of early authors that in compressed air, the circulation is unchanged. The only recent observation on cardiac output is that of Richards and Barach,[143] who could find no change in normal subjects breathing 0.5 atmosphere of oxygen for 1 week; this concentration, however, is usually considered outside the toxic range.

Tinel[165] found that high oxygen caused a constriction of the vessels of the brain. Wolff and Lennox[172] inserted a window over the pial artery of cats and observed a slight decrease in its diameter with 1 atmosphere of oxygen. While breathing a mixture of 90% oxygen and 10% carbon dioxide, the vessels were dilated and the animals showed only the symptoms of carbon dioxide poisoning. When the blood bicarbonate was artificially increased 39% the vessels were constricted, and when the carbon dioxide content was lowered by the intravenous injection of lactic acid, there was dilatation. Cobb and Fremont-Smith[74] studied the retinal circulation in man and found a change in size and color of the veins, but under a mixture

of 90% oxygen and 10% carbon dioxide, so their results cannot be interpreted as due predominantly to the oxygen. Cusick, Benson and Boothby[75] also studied retinal vessels. They found that 30 minutes exposure to 1 atmosphere of oxygen caused a 10 to 38% decrease in the size of the vessels, the greatest change occurring in the veins. Finally, Bean[17,18] directly measured blood flow to the brain through an external cannula in dogs subjected to 4 and 5 atmospheres of oxygen, but could find no change.

The only conclusion that can be drawn from these data is that there appears to be a change in vascular diameter under the influence of high oxygen, but the extent of this change elsewhere than in the brain and its mechanism is not clear.

Metabolism. Measurements of the effect of oxygen pressures up to 1 atmosphere upon the total metabolism are naturally discussed separately from those made at higher pressures. The evidence available indicates that up to 1 atmosphere for relatively short periods oxygen has little or no effect. For example, Hill and Macleod[99] confirming the early work of Bert[10] found that 24 hour exposures to 1 atmosphere of oxygen slightly lowered the CO_2 output of mice. Benedict and Higgins,[39] measuring both CO_2 output and oxygen consumption reported 292 observations of the total metabolism on 6 normal men. They concluded from this abundant evidence that in men in the basal state "breathing 40%, 60%, and 90% oxygen . . . . there is no apparent difference between the metabolism as indicated by the gaseous exchange and the metabolism when breathing ordinary air."

As might be expected owing to additional physical solution, the initial uptake of oxygen by the intact animal rises with increased oxygen pressure. Hence the determination of metabolic oxygen is difficult until a steady state is reached. For this reason some observers have determined total metabolism by measurement of the CO_2 output only. However, Behnke, Johnson, Poppen and Motley,[34] as well as Benedict and Higgins[39] have excluded this factor of physical solution. For example, the former authors found in the case of 4 men breathing 1 atmosphere of oxygen that the oxygen consumption was constant for periods up to 4 hours, at levels not significantly different from the basal uptake as calculated from normal standards. But they did find an increased uptake during the first 20 minutes. They excluded increased physical solution and equilibrium with intestinal gases as the cause, but offered no further explanation.

No systematic studies on metabolism after prolonged (more than 24 hours) treatment with 1 atmosphere of oxygen appear to have been done. Since toxic symptoms usually supervene under these circumstances, changes should be expected. Stadie, Riggs and Haugaard[161] found that the respiration of slices of lung from dogs exposed to 1 atmosphere of oxygen for 48 hours was decreased by 30% from the controls. Loss of weight has been reported by Binger, Faulkner, and Moore,[42] and Smith, Heim, Thomson, and Drinker.[158] However, the usual concomitant anorexia may have been as much responsible as metabolic changes.

Summarizing the metabolic changes, one may conclude that up to 1 atmosphere the inhalation of oxygen for 24 hours produces no significant change in the total metabolism. From the time of the discovery of oxygen by Lavoisier many systems of therapy have been built upon the assumption that the metabolism in normal and diseased states can be altered for the better by the inhalation of high concentrations of oxygen. Aside from the one rational use, *i. e.*, the alleviation of oxygen unsaturation of the blood in pulmonary and cardiac conditions, such conceptions still remain in the

realm of fancy. However, the possibility that lactic acid accumulation, oxygen debt, and so forth can be altered during short periods of vigorous exercise is real and has been discussed by Clark-Kennedy and Owen,[72] and Hill, Long and Lupton.[94]

When the oxygen pressure is raised appreciably above 1 atmosphere the situation is very different. Bert[40] did numerous experiments on rats, mice, sparrows and dogs using both air and oxygen to give partial pressures of oxygen ranging from 1 to 5 atmospheres. "In summary," he stated, "consumption of oxygen, production of carbonic acid and urea, breaking down of glucose in the blood, all chemical phenomena which can be measured easily, appear to be considerably slowed down by the action of oxygen under high tension. And as these are the phenomena which determine the production of heat, it is not surprising to see that the temperature of the animals drops considerably. Nor is it astonishing to see that death is the consequence of such depression in the intensity of the physico-chemical acts of nutrition." (Hitchcocks' translation.) By inference, Bert concluded that the action of oxygen in decreasing metabolic processes is due to its inhibitory effect upon the oxidative enzymes of the tissues (*v. infra*). Hill and Macleod[99] measuring the CO_2 output of mice, rats, and young rabbits, found a decrease at air pressures above 5 atmospheres and at oxygen pressures above 1 atmosphere. This, they concluded, is a constant concomitant of oxygen poisoning. Bean[17,18] also found a definite decrease of oxygen uptake in dogs under 5 atmospheres of oxygen.

Blood Gas Equilibrium. *Oxygen.* The relation between inspired air and blood gases is affected by variations in respiratory movement caused by central nervous system response to toxic levels of oxygen (convulsions), and by possible morphological changes in the alveoli. Hence interpretations of gas equilibria within the organism should be cautious. Nevertheless, Behnke *et al.*[36] have clearly demonstrated a prompt equilibrium between alveolar and pulmonary blood oxygen in dogs under 4 atmospheres of oxygen.

Carbon Dioxide. In the problem of blood and tissue carbon dioxide under high oxygen, the Reviewers believe that there has been in the literature an unfortunate and erroneous use of the word "retention." They define retention as an *accumulation* of carbon dioxide in blood or tissues owing either to impaired transportation or faulty elimination. They distinguish from this an increase in the partial pressure of *free* carbon dioxide, which does not necessarily mean retention as will be pointed out later. They further distinguish retention from *diminished metabolic formation*. Without these distinctions, discussion of the literature becomes confusing.

The question of carbon dioxide output under high oxygen must be discussed in the light of: (1) possible associated change of total metabolism, or (2) true carbon dioxide retention. While there are many experiments showing that carbon dioxide output is diminished under moderate oxygen pressures (0.8 to 2 atmospheres), concomitant studies on oxygen uptake have as a rule not been made, hence decrease in metabolism cannot be eliminated as the cause. Such experiments were reported by Bert,[40] Achard, Binet and Leblanc,[1] Achard, Leblanc and Binet,[2] and Becker-Freysang and Clamann.[27] On the other hand, Hill and his co-workers,[95] in experiments at these relatively low pressures, while finding similarly diminished carbon dioxide output, also noted an associated fall in body temperature sufficient to indicate a markedly lowered metabolism. In other words, there is no evidence of a true carbon dioxide retention under

these conditions; rather, decreased metabolism is a sufficient explanation. However, Hill suggested pulmonary damage as the cause. While this might easily explain an increase in the partial pressure of blood or tissue carbon dioxide as observed in other types of pulmonary pathology, it could only explain a temporary and not a persistent diminution of carbon dioxide elimination and even less, the increasing diminution which Hill observed. Furthermore, there is no evidence that true retention of carbon dioxide as we have defined it occurs even under pressures of oxygen greater than 2 atmospheres. In fact, Behnke *et al.*[36] demonstrated in dogs that exposure to 3.8 atmospheres does not significantly alter the *arterial* P_{CO_2}, in sharp contrast to the increased P_{CO_2} of the *venous* blood generally observed. In the Reviewers' opinion this is proof that there is no interference with carbon dioxide transportation or elimination. Finally, Behnke and Stephenson,[37] quoting their own unpublished experiments, were "unable to demonstrate any retardation in the elimination of carbon dioxide from the tissues" under high pressures of oxygen.

On the other hand, there is clear evidence that the *partial pressure* of carbon dioxide in the tissues is *increased* by high oxygen. Hill,[96] Gesell,[88] Campbell[59–61] and Behnke *et al.*[36] all found an elevation of P_{CO_2} in tissues and *venous* blood. A consideration of the full evidence outlined above, particularly that of Behnke, has brought the Reviewers to the conclusion that this increased CO_2 pressure is not due to retention as they have defined it. In their opinion the interesting and unique change in the acid-base balance of the blood known as the loss of the dual function of hemoglobin, first outlined by Gesell,[88] is a sufficient explanation. This is discussed more fully later.

Summarizing data on blood gas equilibrium, while there is evidence that high oxygen pressure produces a decrease in oxygen uptake, and *pari passu* in carbon dioxide output, these changes can be fully explained on the basis of lowered general metabolism. Changes in the partial pressure of carbon dioxide constitute a separate problem, accountable for, we believe, by Gesell's hypothesis.

Influencing Factors. *Gases.* At the outset, the distinction must be clearly drawn between the specific effects of high pressures of gases other than oxygen, and the effects which such gases produce on the toxicity of oxygen. In the first case, for example, the well-known narcotic effect of nitrogen at high pressures of air characterized by stupor, mental torpor, and so forth might be so great *per se* as to obscure more or less the effects of oxygen. Thus, Behnke, Thomson and Motley[38] contrasted the above-mentioned symptoms of narcosis produced by 3 to 10 atmospheres of air pressure with the convulsions, syncope, and so forth described by Behnke *et al.*[34] as accompanying 4 atmospheres of oxygen. They infer that under air pressure, the symptoms are largely those of nitrogen narcosis. They were confirmed in this conclusion by the experiments of Case and Haldane.[69] No experiments have been reported which would suggest any influence of nitrogen upon the toxicity of oxygen. These specific effects of gases other than oxygen do not fall within the scope of this review, but are mentioned in order to make the distinction clear.

Possible toxic action of contaminants of cylinder oxygen as causal agents has been excluded by the early work of Bert,[40] who found symptoms with cylinder oxygen or compressed air to be solely a function of the partial pressure of the oxygen. Binger, Faulkner and Moore,[42] in studies on rabbits, also excluded ozone as a possible cause of poisoning.

The most important gas to be considered in conjunction with oxygen is

carbon dioxide, because it figures largely in Gesell's discussion of the "dual function of hemoglobin" (*q.v.*). Gesell's hypothesis states that oxygen at high tensions increases the sensitivity of the animal to the administration of carbon dioxide owing to the broken coördination of the dual function of hemoglobin. This leads to acidosis which is further augmented by the administration of carbon dioxide, as he found to be the case in experiments on rats. The opposite explanation is offered by the observations of Shaw, Behnke and Messer[151] who produced subnormal levels of alveolar carbon dioxide tension by artificial hyperventilation, and supernormal levels by increasing the carbon dioxide in the mixture breathed, in dogs subjected to from 1 to 4 atmospheres of oxygen. Although the signs of oxygen poisoning appeared with subnormal alveolar carbon dioxide, they were hastened by an elevated carbon dioxide. The authors found, like Gesell, that elevated tensions of carbon dioxide which were not toxic at 1 atmosphere became associated with toxic symptoms in the presence of 4 atmospheres of oxygen; but, unlike Gesell, concluded that carbon dioxide might increase the toxicity of the oxygen or the sensitivity of the tissues to oxygen. However, it is obvious that no choice can be made between the two explanations on the basis of these experiments. In any case, since toxic symptoms of oxygen were found at subnormal levels of alveolar carbon dioxide, Shaw, Behnke and Messer concluded that carbon dioxide plays only a secondary rôle in oxygen poisoning. (For further discussion, see the sections on the Dual Function of Hemoglobin and Metabolism.)

In a more restricted experiment, discussed elsewhere with the question of circulation, Wolff and Lennox[172] found very slight arterial contraction under the influence of pure oxygen, and distinct dilatation when 10% carbon dioxide was added. In this respect, then, carbon dioxide appears to exert an influence exactly opposite to that of oxygen.

Hill[96] exposed monkeys, guinea pigs, rats, and goats to a mixture of 5% carbon dioxide in 1 atmosphere of oxygen, and then oxygen up to 5 atmospheres. The result was that the critical pressure of oxygen needed to produce convulsions within a given time, and the time necessary to produce them at a given oxygen pressure, were both distinctly lowered. He concluded that an "increase in carbon dioxide tension in the tissues is a factor in the production of convulsions which follow exposure to high pressures of oxygen." The same result was achieved by Massart[127] on mice, using 5% carbon dioxide in oxygen at 4 atmospheres, but his explanation is that respirations are increased (by the carbon dioxide) and hence there is a more rapid arrival at equilibrium with the oxygen. This explanation is untenable in view of the facts that respiratory rate is not materially affected by high air pressures (see the section on Symptoms), and that alveolar and blood oxygen are in equilibrium when pure oxygen is breathed (Behnke *et al.*[36]). The acceleration of oxygen toxicity by admixed carbon dioxide was also observed by Hederer and Andre.[91]

Libbrecht and Massart,[121] in an unconfirmed single report, stated that hydrogen had an antagonistic action to that of oxygen at high pressures. Mice, which had severe convulsions at 4 atmospheres of pure oxygen, when subjected to the same oxygen pressure plus 6 atmospheres of hydrogen, developed no convulsion but severe pulmonary symptoms only, although in the latter case the animals died sooner. This would indicate that the hydrogen acts as antagonist only to the effects of oxygen upon the nervous system as distinguished from those upon the pulmonary system.

Other Factors. Paul Bert[40] first observed, in conjunction with the general slowing of physiologic processes under compressed air, that body tempera-

ture was lowered. Hill[95] confirmed this, and made the further observation, which is difficult to explain in the light of later experiments, that he could protect animals to some extent by warming the pressure chamber. The first suggestion of the opposite effect of external temperature was given by Faulkner and Binger[82] who found that while turtles were more resistant than warm-blooded animals to 0.9 atmosphere of oxygen ordinarily, they became fully as susceptible to lung damage when the temperature was raised to 37.5° C. Perhaps this is owing to the increased metabolism of poikilothermous animals at elevated temperatures, a well-known phenomenon. Later, Campbell[62–64] made quantitative studies of the temperature effect on rats and found that a decrease in body temperature of about 10° C. increased the survival factor by about 10 times at pressures up to 6 atmospheres. The only temperature studies on men that have been done were concerned with the effects of carbon dioxide and nitrogen in compressed air, by Case and Haldane.[69]

One would expect that muscular exercise would alter the effects of high oxygen pressures, but no thorough investigations have been directed at this question. However, Bornstein and Stroink,[48] while finding no symptoms in themselves at rest in 45 minutes at 2 atmospheres, brought on cramps, clonic muscular spasms and hyperactivity of deep reflexes by exercises. Hill, Long and Lupton[94] studied the effect of exercise in man, but only at the non-toxic level of 0.5 atmosphere; they found a 10 to 50% increase in oxygen uptake, which was not due to increased saturation of the blood. It would be valuable to extend this investigation to higher concentrations of oxygen.

A number of drugs have been found to affect oxygen poisoning. The first investigation of drugs by Campbell[59] disclosed no effect by thyroid medication, although in later works,[63,65,66] he found that thyroxin and to a lesser degree certain other drugs, definitely enhanced the effect of oxygen on rats. In substantiation, he also found that the survival rate was increased following either thyroidectomy or hypophysectomy (to remove the thyrotropic effect of the posterior pituitary). He found that histamine had no effect (see section on Circulating Blood), but that oxygen poisoning was increased by dinitrophenol, ac-tetrahydro-beta-naphthylamine, adrenalin, extract of the posterior lobe of the pituitary, insulin, eserine and atropine. Marshall and Rosenfeld[126] found that oxygen increased the depression of respiration caused by anesthetics (including barbiturates and morphine, but not chlorbutanol, urethane, paraldehyde or alcohol) apparently by removing otherwise effective anoxemic stimuli which act through the sino-aortic mechanism. On the other hand, addition of carbon dioxide to the oxygen failed to prevent this enhanced depression, which suggests an effect due to a specific action of oxygen. A conflicting observation was made by Hederer and Andre[91] that barbiturates retarded the convulsions produced by oxygen, but as might be expected, strychnine enhanced them.

Finally, Campbell[62] and de Almeida[78,79] both found a marked increase in resistance to oxygen in rats that had been starved, and Smith *et al.*[158] found that the tolerance of rats was decreased late in pregnancy.

In summary, there are several factors which influence oxygen poisoning. Carbon dioxide clearly exerts an influence, apparently secondary, either by enhancing the effect of oxygen, or by contributing an independent effect enhanced by the oxygen. There is some evidence that it counteracts peripheral vascular contraction by oxygen but to what extent the latter occurs is not clear. Hydrogen appears to retard the effects of high

oxygen pressures, but there is no evidence as to an effect by nitrogen. Oxygen poisoning has been well shown to be diminished by a lowered body temperature, and *vice versa*, as well as by starvation, but to be augmented by several drugs, notably thyroxin and certain respiratory depressants.

Tolerance, Adaptation and Oxygen Therapy. Any discussion of oxygen poisoning naturally requires consideration of the maximum non-deleterious dose of oxygen at various pressures above the normal of 0.2 atmosphere. The observations in the case of man are more complete and consistent than those for other species, and will be considered first because of their importance.

The lowest concentration of oxygen at which physiologic changes have been noticed was reported as 45% by Richards and Barach,[143] who found that 2 normal subjects kept at this level for a week showed a fall in pulse rate and a slight rise in total carbon dioxide content of the blood. There were no changes in respiratory metabolism, cardiac output or excretion of electrolytes and water. Patients with cardiac insufficiency, however, showed good therapeutic response to oxygen at 0.4 to 0.5 atmosphere for periods up to 7 months without demonstrable signs of oxygen poisoning.[144] Binet *et al.*[41] described some minor physiologic changes in rabbits at 0.6 atmosphere. With these exceptions, the maximum oxygen concentration that can be inhaled by man and other warm-blooded species indefinitely without harm was given as approximately 0.6 atmosphere by Barach,[14] Boycott and Oakley,[50] Binet *et al.*,[41] Behnke and Shaw,[35] Becker-Freysang and Clamann[27] and Trusler and Meiks.[166]

Recently developed methods have made possible the use of oxygen at nearly 1 atmosphere for certain purposes, as described for example by Boothby[46] and Boothby, Mayo and Lovelace.[47] Behnke *et al.*[34] described symptoms occurring in 0.96 atmosphere oxygen at various times up to about 4 hours, which they gave as the limit of safe exposure. The important observation of Marshall and Rosenfeld[126] was discussed above, that under certain conditions of respiratory depression by anesthetics, the administration of oxygen will further depress respiration. While Anthony[9] and Anthony and Beudenkopf[10] describe a fall in the number of blood cells and hemoglobin produced by inhalation of approximately 1 atmosphere of oxygen for periods as short as 15 minutes, it is doubtful whether this can be considered a toxic effect, since it is reversible and was not reported as accompanied by symptoms. Fine, Hermanson and Frehling[83] reported no toxic symptoms from the use of 0.95 atmosphere of oxygen when the patients were taken out of the tents at least ½ hour out of every 4 to 8 hours. Schwartz and Malikiosis[149] reported the sudden development of clonic spasms and collapse in subjects who were given 1 atmosphere of oxygen following a period of breathing air at diminished pressure. Boothby[46] concluded that oxygen at 1 atmosphere may be administered for 24 hours, and Boothby, Mayo and Lovelace[47] reported the administration of 1 atmosphere of oxygen to 800 patients with no evidence of the development of pulmonary irritation in less than 48 hours, and none in several days with intermittent administration. Whether in all cases these patients were inhaling 1 atmosphere of oxygen is uncertain since the report gives no analyses of circumambient oxygen. Furthermore, the important factor of intermittence for feeding, medication, and so forth was not included in the data. The authors recommend, in conclusion, that 1 atmosphere of oxygen may be given for 36 to 40 hours, but then must be reduced to 0.6 atmosphere. Becker-Freysang and Clamann[27] felt no symptoms for 24 hours in 0.9 atmosphere of oxygen. Behnke,[28] on the other hand,

found that healthy males show a slowing of the pulse rate and pallor in 7 hours at 1 atmosphere, and beyond this time, an increase in respiratory depth with nausea and flushing. In a later paper, Behnke[30] stated that 1 atmosphere can in most cases be inhaled for 17 hours without injury, although some subjects have complained of substernal distress in 7 hours, and 1 subject developed an allergic response. Moody and Howard,[122] using an oxygen tent, observed, as previously mentioned, convulsions in a child, who spent 6 days intermittently in an atmosphere which, although not measured, was assumed to be in excess of 0.7 atmosphere of oxygen. The child, 2 years old, had pneumonia and had given a good response to sulfonamide therapy with the exception that cyanosis had persisted. The convulsions were relieved by removal from the tent, recurred on re-entrance, and were again relieved on removal. For this reason, and because of the absence of any other abnormal findings including fever, they were attributed to the oxygen.

The conservative conclusion by the great majority of those experienced in oxygen therapy is that 0.6 atmosphere of oxygen is relatively safe for an indefinite period, and 1 atmosphere for about 24 hours, with due consideration for the factors discussed elsewhere. Ruff and Strughold, quoted by Becker-Freysang and Clamann,[27] described what they called the "paradoxical oxygen effect." Subjects breathing oxygen at 1 atmosphere for a period of time, when transferred to air at somewhat diminished pressure, developed clonic spasms and collapse. This phenomenon has been observed in interceptor pilots who breathe oxygen at ground level for purposes of de-nitrogenation and then ascend quickly to high altitudes. It probably is not related to the problem of oxygen poisoning, but is perhaps explainable in the light of the observations of Watt, Dumke and Comroe,[168] discussed in the section on Respiratory Symptoms.

Young animals appear to be relatively resistant to the toxic action of high pressures of oxygen.[91,157] For example, Smith, Bennett, Heim, Thomson and Drinker[157] found that young rats were not so readily poisoned by exposures to 0.8 to 1 atmosphere of oxygen as were older ones, a fact which they were inclined to attribute to morphologic differences in pulmonary structure. This increased tolerance has also been observed in the human by Chapple.* Employing a special incubator[69a] which permitted treatment without intermittence at oxygen pressures never less than 0.85 atmosphere, he has treated premature infants weighing less than 3 lbs. for periods frequently as long as 3 weeks. During treatment the humidity is maintained close to 100%. Under these circumstances, he observed no poisonous action of oxygen whatever, and is convinced that this form of oxygen therapy is of great value in this type of case.

It has been suggested that part of the deleterious action of oxygen especially upon the lungs may be due to its dryness when administered. No papers discussing the possible relation of humidity to oxygen poisoning have been found.

The few conflicting reports concerning adaptation are mentioned in the discussion of morphology and circulating blood, and allow only the conclusion that if adaptation occurs, it is due to the protective action of pulmonary pathology, and possibly, as pointed out by Campbell,[60] to the decrease in hemoglobin and red cells (*v. supra*).

In connection with the use of oxygen at pressures about 1 atmosphere,

* Dr. Charles C. Chapple, of the Department of Pediatrics, University of Pennsylvania, has courteously permitted us to quote his work in advance of its publication in this Journal.

for example in preliminary de-nitrogenation of divers, Behnke and Shaw[35] have emphasized the importance of a thorough knowledge of tolerance levels. In view of the scattered nature and inconsistency of the observations at higher pressures, particularly in animals, the summary given in Table 1 of tolerance levels found by various investigators will serve as useful a purpose as an extended discussion of all the reports. As was pointed out earlier, the safe time limit can be seen to drop with increasing rapidity as the oxygen pressure is raised above 1 atmosphere. One explanation for this phenomenon, which supposes a protective effect at low pressures by pulmonary pathology, is discussed in the section on Pathology. It can also be seen by inspection of the table that there is a *marked variation in tolerance to oxygen among different species.* For example, while most mammalians have almost instantaneous convulsions at 5 atmospheres, Cleveland's observations[73] on cold-blooded vertebrates show a markedly greater tolerance of these species.

TABLE 1.—A COMPARISON OF THE LEVELS OF OXYGEN POISONOUS TO VARIOUS SPECIES, FROM AVERAGE FIGURES IN THE LITERATURE

Oxygen tension (atmospheres)	Animal species	Lethal time (hrs.)	Asymptomatic time limit for man	Reference numbers
0.45	.....	...	7 days	95, 143
0.6	.....	...	Indefinite	14, 27, 35, 41
0.7+	.....	...	6 days	49, 132, 166
0.8	Rabbit	192	...	14, 42
0.85 to 1	Premature infants	...	> 3 weeks	Chapple (personal communication)
0.89 to 0.9	Mouse	36	24 hours	27, 140
	Dog	120	...	136, 137
0.95 to 0.96	Rat	144	...	34, 57, 154
	Cat	72	...	136, 137, 140
	Dog	108		
0.99 to 1	Dog	48	7 to 40 hr.	28, 30, 34, 46, 47, 136, 137, 140
2.0	Mammalians	4	0.75 to 3 hr.	34, 48, 96
3.0	.....	...	0.50 to 2	34, 96, 109
3.5	Frogs	65	...	73
	Salamanders and goldfish	50 to 60	...	73
4.0	Mammalians	0.48	0.20 to 0.70	34, 96, 164
5.0	Mammalians	0 to 2 (rats)	...	48, 96
7.0	.....	...	0.10	90
8.0	Rats	0	...	48
9.0	.....	...	0.05	109
50.0	Rats, mice, etc.	0	...	99

One may conclude that the maximum non-deleterious dose of oxygen which can be used for indefinite periods appears to be 0.6 atmosphere, while for 1 atmosphere the time limit is 24 hours. Chapple's experience (*v. supra*) would appear to exclude premature infants from these limitations. The evidence is not sufficient to say that adaptation occurs to an important degree. Tolerance to high oxygen decreases rapidly with increasing pressures above 1 atmosphere, and is in general lowest for mammalians and greatest for cold-blooded species.

Oxygen Aero-embolism From Rapid Decompression. There is a sole report in the literature: Hill,[95] in experiments on toads, rats and guinea pigs, showed the formation of bubbles in the heart and other organs following rapid decompression from high pressures of pure oxygen, but the

pressures used were very high, namely, 15 to 20 atmospheres. It is probable that decompression from lower pressures (2 to 5 atmospheres) would not be accompanied by aero-embolism, because oxygen, unlike nitrogen, is rapidly used for metabolic purposes and therefore would most probably not persist, to form gas emboli.

Isolated Surviving Tissue. The experimental work in this category is limited. Bert (1878)[40] reported that the oxygen uptake and CO_2 output of strips of beef muscle, when subjected to high oxygen, was diminished compared to controls.

Most of our later knowledge of this phase of the subject is due to the excellent series of papers by Bean and his associates. Bean and Bohr[23] found in the case of smooth muscle (duodenal and pyloric sphincter muscle of rabbits) subjected to 6 atmospheres of oxygen, a definite pattern of low peristalsis and spasm similar to that produced by HCN but different from that by atropine. He concluded that this was owing to a direct action of oxygen upon the enzymatic systems of the tissues resulting in low oxygen utilization, a condition which he called "hyperoxic anoxia." The effect was reversible only after comparatively short exposure to relatively low pressures; no reversibility occurred after exposure to high pressures. With radial beef iris muscle, Bean and Bohr[22] observed a decrease of tonus when the muscle was subjected to 4.8 atmospheres of oxygen. Controls in air at the same pressure were unaffected. Recovery of normal tone followed removal from the high pressure. Atropinization did not change the effect of high oxygen. The authors concluded that the pupillary dilatation observed at high pressures of oxygen is not necessarily dependent on central nervous or hematogenous connections. Studying mammalian smooth muscle (rabbit duodenal strips) Bohr and Bean[44] found a decrease of tonus after 2.5 hours at 6 atmospheres of oxygen. Reversal to normal occurred if the high oxygen period was relatively short, but otherwise a periodic tonic spasm supervened. They stated that the action is not due to an epinephrine-like substance at the myoneural junction. Bohr and Bean[43] studied the action of the isolated frog heart in 5 atmospheres of oxygen. They found an initial increase followed by a delayed slight decrease in the strength of the beat. Later there was a loss of automaticity, but irritability remained even after the beat had ceased. Recovery after decompression was observed if the experiment was terminated before the complete cessation of cardiac activity.

The same authors,[21] using isolated striated muscle of the frog, found after exposure for 1.5 to 5 hours to oxygen at 5 atmospheres an initial increase of contraction followed, however, by a marked decrease in response to electrical stimulation of muscle or nerve compared to controls in air at elevated pressures. Usually no recovery was observed after 2 exposures. Their data led them to believe that the effect is mainly if not all upon the muscle rather than the nerve fiber or the myoneural junction. Hill and Macleod[99] found that the thin sartorius muscle of the frog, after 1 hour exposure to 50 atmospheres of oxygen, showed a greatly diminished height of contraction and a prolonged latent period. The gastrocnemius muscle, however, appeared relatively little affected.

Bean and Bohr,[21] in discussing the problem of oxygen poisoning, laid considerable stress upon the loss of the dual function of hemoglobin as the main cause of tissue dysfunction. They attributed to the "accumulated carbon dioxide and acidity resulting from inadequate reduction of hemoglobin a more significant etiologic factor in the early signs and later events of oxygen poisoning" than the "direct" toxic action of high oxygen upon

the enzyme systems involved in metabolic processes. This aspect of the subject is discussed more fully later.

Hill and Macleod[99] observed that a frog's heart continued to beat after 1 hour's exposure to an oxygen pressure of 50 atmospheres. Cold-blooded animals are known to be relatively resistant to oxygen poisoning, nevertheless this is an extraordinarily high pressure of oxygen to be survived by tissues.

Burrows[54] found in the case of tissues from chick embryos that the rate of growth is slightly more rapid in an atmosphere of pure oxygen, but the total growth is no greater than at lower partial pressures. He did not study the effect of pressures greater than 1 atmosphere.

Summarizing the only evidence available on isolated surviving tissue, it shows a distinct decrease in the function of smooth and striated muscle, but no apparent effect on myoneural junctions. Other tissues have not yet been sufficiently studied to warrant a conclusion.

Neoplasia. A brief chapter on this subject has accumulated in the literature. Fischer and Andersen[84] reported that under increased oxygen pressure sarcoma cells were killed more quickly than normal tissue cells in artificial culture media. Their data, however, are not convincing. Later, Andersen and Demuth,[8] experimenting on 500 mice, reported that in some animals pre-treated intravenously with copper or selenium (having tumor affinity and possibly catalytic action) and kept in 1.5 to 2 atmospheres of oxygen for 24 hours, transplanted carcinomata could be made to disappear completely. Oxygen or the metal alone did not give the effect. Occasionally permanent recovery followed, but in most cases the tumor reappeared from incompletely necrotized tissue. Still later, Fischer and Andersen[85] again found with transplanted tumor in mice that treatment for 24 hours with 1 atmosphere of oxygen resulted in the disappearance of the tumor. Better results were obtained when the oxygen treatment was combined with copper or selenium injections. However, these results were obtained only if the treatment was given during the first week after the transplantation and they surmised that similar therapeutic success is doubtful in the case of humans. De Almeida,[79] using starved rats to increase oxygen resistance, found that sarcoma (fusiform cell type of Ruffo) could be made to disappear following treatment with oxygen at 1 to 8 atmospheres for 24 hours to 20 minutes. His best results were obtained with 6 atmospheres of oxygen for 2 hours. The tumors were completely destroyed by a single treatment; 10 days later they were red, impregnated with blood, and microscopically none of the tumor tissue was preserved. De Almeida expressed intentions of building a chamber for the treatment of human cases to be reported on later. We have been unable to find further reference to such work. Campbell[58] subjected de Almeida's work to close scrutiny. Using Bashford's mouse carcinoma (No. 63), Twort's mouse tumor, or Walker rat tumor, he was unable to demonstrate any effect upon the histology after treatment of the animals with 4 to 5 atmospheres of oxygen for 1 hour. Nor was any effect found on spontaneous mouse mammary carcinoma.

The possibility, then, that high oxygen pressures might differentially injure or kill malignant cells either in culture or *in situ* remains unsettled in view of these interesting but conflicting reports.

Plants and Microörganisms. Scattered observations indicate a toxic action of high oxygen pressure upon forms of life other than mammalian. Bean,[19,20] for example, observed that the growth of pneumococcus is a function of the oxygen pressure, being maximum at about 1.2 atmospheres

and then declining, to cease at a pressure of about 2 atmospheres. The organisms could be killed by exposures to 5.8 atmospheres for 1 to 2 hours.

Boothby[46] discussed the possibility of the bactericidal action of oxygen at 1 atmosphere in cases of gas gangrene and tetanus.

Karsner, Brittingham and Richardson[114] found that the growth of most of the common pathogenic bacteria is inhibited by 1 atmosphere of oxygen. The pneumococcus was an exception.

Novy and Soule,[134] studying the tubercle bacillus, observed excellent growth at 0.4 to 0.5 atmosphere of oxygen but reported definite inhibition at 0.8 to 1 atmosphere.

Rahn and Richardson[142] studied the growth of *Streptococcus lacticus*, *Pseudomonas fluorescens* and *Bacillus subtilis* under high oxygen pressures. The first was greatly inhibited by oxygen at 1 atmosphere. The others were uninfluenced.

Thaysen[163] reported that the growth of a number of common organisms was greatly retarded at 10 atmospheres of oxygen. The effect was dependent upon the temperature, being lethal if the temperature was raised slightly above the optimum for growth. This observation is similar to those on higher organisms, discussed elsewhere.

Massart[128] reported that the respiration of yeast was decreased by exposures to 3 to 5 atmospheres for short periods of time (15 to 60 minutes). He attributed this to a partially irreversible oxidation of cytochrome which in the oxidized state, he assumed, is without respiratory function. Albaum, Kaiser, and Eichel[6] showed that oat grains soaked for 24 to 48 hours in water saturated with oxygen at 1 atmosphere manifested inhibited growth. Albaum, Donelly and Korkes[5] found a similar effect with oat seedlings associated with a lowered catalase and endogenous dehydrogenase activity. Cleveland,[73] in an interesting paper, reported that intestinal protozoa infesting termites, earthworms, cockroaches, frogs, salamanders and goldfish, were killed *in situ* by 3.5 atmospheres of oxygen without injury to the hosts. However, intestinal trichomonas of rats or man were not killed *in vitro* by such pressures.

Summarizing the evidence on microörganisms, high oxygen causes toxic effects which are similarly enhanced by elevated temperature, upon them as upon vertebrates.

Dual Function of Hemoglobin. The expected increase of saturation of arterial and particularly venous blood resulting from high oxygen pressure was first observed by Bert[40] and confirmed in extensive studies on human subjects by Hill.[95] Increase of physically dissolved oxygen as well was demonstrated by Wolff and Lennox[172] in cats at about 1 atmosphere, and by Behnke *et al.*, whose experiments are fully discussed below.

One hypothesis explaining the toxic effect of excess oxygen in the intact mammalian organism resulting from these observations, and first proposed by Gesell,[88,89] postulates that part of the "dual function" of hemoglobin is lost owing to the fact that blood oxygen in physical solution is sufficient in whole or in part for metabolic needs; hence little or none is supplied by reduction of the hemoglobin. The mechanism by which this loss produces its effects is illustrated by Figure 1. This shows the relation between the total CO_2, the pH, and P_{CO_2} of the whole blood. The *arterial* point, *A*, is on the totally oxygenated line, and the blood (the subject breathing air) contains 50 vol. % of CO_2, the pH = 7.400 and the P_{CO_2} is 40 mm. Hg. (Assume for simplicity that the blood is 100% saturated and contains hemoglobin equivalent to 20 vols. % of oxygen.) The venous point is derived thus: in the normal subject at rest, the mean CO_2 content

of *venous* blood is 55 vols. %, approximately 5 vols. % greater than the CO_2 of *arterial* blood. If the respiratory quotient is average, *i. e.*, 0.8, there will be 5/0.8 = 6.2 vols. of oxygen consumed per 100 cc. of blood. The blood will then be 69% saturated, and the CO_2-pH line of the whole blood will be that indicated by the dashed line intermediate between the fully oxygenated and fully reduced lines. Hence the *venous* point will be

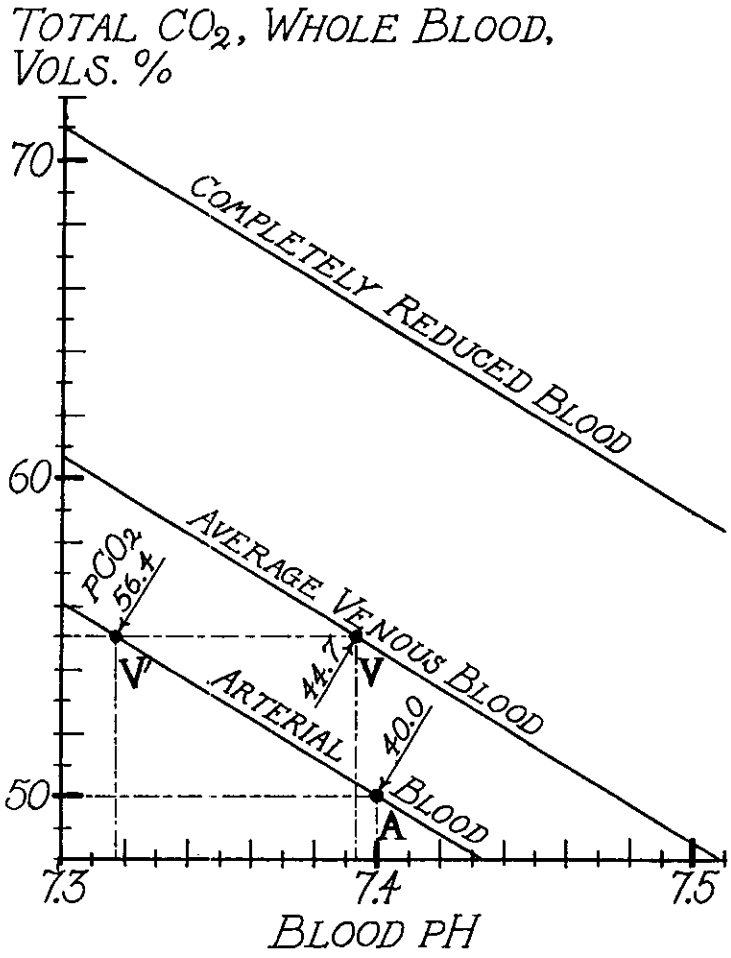

FIG. 1.—Schematic diagram illustrating the loss of the dual function of hemoglobin when sufficient oxygen (2.6 atmospheres) is inhaled to supply metabolic needs by physical solution.

at *V*. The pH and P_{CO_2} will then be 7.395 and 44.7 mm. Hg respectively. By reduction of the hemoglobin, 4.73 vols. % of CO_2 (95% of the total) are taken up without any change in pH, while only 0.27 vols. % (5% of the total) are taken up by the pure buffer action of the blood. The pH change is thus very small, *i. e.*, only 0.005 pH. The situation is quite different if the subject is breathing oxygen under increased pressure. For example, the solubility of oxygen in water is 2.4 vols. % per atmosphere

and hence (neglecting the diminished solubility in blood since the calculations are approximate and illustrative only) at 6.2/2.4 = 2.6 atmospheres oxygen pressure the oxygen in physical solution alone would be sufficient to take care of the metabolic needs. There would be no reduction of the hemoglobin whatever and the line showing the relation between total CO_2 and pH of the venous blood would be the fully oxygenated one. The venous point would then be at V' and the pH and the P_{CO_2} would be 7.317 and 56.4 mm. Hg respectively. The elimination, owing to the presence of sufficient physically dissolved oxygen for metabolic needs, of this important function of hemoglobin, namely, release o' base upon reduction, increases the changes of the pH by 0.078 and of P_{CO_2} by 11.7 mm. Hg beyond those occurring normally. The increased metabolism of exercise does not affect the above conclusions. For it is easy to show, on physicochemical grounds only, that when the CO_2 output and oxygen uptake increase *pari passu* the calculated values of pH and P_{CO_2} of the venous blood are essentially those given for the basal state.

If this mechanism is the sole one operating when oxygen at high pressures (>2.6 atmospheres) is inhaled, we would expect to find a decrease below the normal venous pH of about 0.08, and an increased venous partial pressure of CO_2 of about 12 mm. Hg. Bean,[18] using the manganese dioxide electrode, was successful in measuring such changes of pH of blood in dogs breathing oxygen at elevated pressures, the venous blood being arterial in color. No P_{CO_2} values were reported. Bean, in agreement with Gesell, attributed considerable significance to these changes. Campbell has reported extensive observations on the partial pressure of CO_2 in the tissues of animals breathing air, and oxygen under high pressures. He injected bubbles of air or nitrogen into tissues or into the peritoneal cavity and after sufficient time had elapsed for equilibration with tissue CO_2, removed the gas for analysis. He found quite consistently, compared to normal conditions, that under high oxygen tensions the partial pressure of the CO_2 in tissue was elevated by 15 to 20%. This led him to conclude that a major effect of oxygen poisoning is a "retention" of free carbon dioxide by the tissues. Paine, Lynn and Keys,[137] on the other hand, studying the gases in artificially obstructed intestinal loops of dogs in 1 atmosphere of oxygen, found no changes in the carbon dioxide levels from those found in similar animals breathing air, although the oxygen tensions rose as was anticipated. These observations are suggestive, but the critical experiment to test Gesell's hypothesis requires determination by the glass electrode of the actual pH, the analysis of the arterial and venous blood for total CO_2, and the calculation from these data of the P_{CO_2} of the venous and arterial blood under conditions of high oxygen pressure.

Behnke *et al.*[36] have approached this ideal experiment so closely that their observations may be accepted with confidence. Arterial and venous blood from dogs under high oxygen pressures was analyzed for total CO_2. Samples of the same blood were then equilibrated with known pressures of CO_2 and the total CO_2 content determined. From these data the authors constructed log CO_2—log P_{CO_2} lines according to the method of Peters,[139] and by interpolation determined the P_{CO_2} of the original arterial or venous samples. The pH values could then be calculated by the use of the familiar Henderson-Hasselbach equation. Although indirect, this method of calculation rests upon a sound basis. Behnke reports the following findings in the case of 9 dogs breathing oxygen at about 3.8 atmospheres:

1. In all cases the venous oxygen content was equal to or greater than the oxygen capacity indicating that the entire metabolic oxygen was supplied by physically dissolved oxygen. That is to say, there was no reduction of the hemoglobin and the mechanism under consideration was operative.

2. The arterial P_{CO_2} was either the same (7 observations) or slightly lower than when breathing air. This is proof that carbon dioxide *transport* is not interfered with.

3. The venous P_{CO_2} was significantly higher than the controls breathing air by an amount averaging 6.5 mm. Hg greater than the controls.

4. The pH of the arterial blood was unchanged whereas that of the venous was less but by a small amount averaging about 0.03 unit.

Behnke concluded from these data that this unique form of CO_2 acidosis expected on physico-chemical grounds does occur but that it is slight, and he dismisses this loss of the dual function of hemoglobin from consideration as a causal factor in oxygen poisoning.

The reasons given by Behnke (somewhat extended by the authors) are: (1) the familiar symptoms of CO_2 acidosis do not resemble remotely those of oxygen poisoning; (2) the changes observed are slight; (3) according to the theory maximal oxygen poisoning should be reached at 2.6 atmospheres, since at this pressure the dual function is completely lost. But Behnke emphasized that oxygen poisoning frequently does not develop promptly at pressures of 3 to 4 atmospheres despite this complete loss. Only 2 out of 9 of his dogs had convulsions even when the hemoglobin of the venous blood was completely saturated. Moreover, Behnke and others have reported that at higher pressures (4 to 6 atmospheres) toxic symptoms are severer and occur sooner than at lower pressures (see section on Tolerance).

One may conclude from the evidence at hand that the changes in the blood expected on physico-chemical grounds do occur when excess oxygen is inhaled, but that they play little or no rôle in the picture of oxygen poisoning.

Enzymatic Systems. The conviction is growing that the action of oxygen is upon the enzyme systems of cells resulting in reversible or irreversible changes such that serious impairment of essential cellular metabolic functions results. The idea goes back at least to Paul Bert's time: Although he found that pressures of oxygen up to 15 atmospheres had no influence upon the activity of such enzymes as salivary diastase, pepsin, invertase, emulsin and myrosinase, he did show that a strip of beef muscle suspended in oxygen at similar pressures showed diminished oxygen and CO_2 metabolism compared to controls under normal conditions. He also found that putrefaction was delayed or inhibited by high oxygen pressures.

The literature on the action of high oxygen upon enzymes may for convenience be discussed in two parts: (1) scattered, relatively non-systematized observations showing the effect of oxygen upon sundry enzymes: (2) more or less systematized studies upon one enzyme forming the basis of an hypothesis explaining oxygen poisoning. These latter are discussed in connection with the hypotheses proposed.

The enumeration of the scattered studies follows:

Confirming Bert's observation on enzymatic autolysis are the studies of Bailey *et al.*[13] and also Laquer.[117] McCance,[129,130] however, found that the effect of aërobic autolysis was mainly upon urea formation which was diminished under oxygen. Meyer[131] showed that the ability of mouse brain homogenates to oxidize guaiacum in the presence of hydrogen per-

oxide was greatly diminished by a preliminary exposure to 4 atmospheres of oxygen for 4 hours. Shapiro and Wertheimer[150] reported that fatty acid dehydrogenase demonstrated by the Thunberg technique in rat tissue is peculiarly susceptible to short exposures to oxygen. Marks,[123,124] and Marks and Fox[125] found that the catalase activity of extracts from marine animals and plants compared to anaërobic controls is significantly diminished by prolonged exposure (1 to 2 days) to air or oxygen. However, oxygen inactivation of catalase is very slow (20 days for complete inactivation at 25° C.).

One difficulty in interpreting the effects of oxygen upon enzymes is illustrated in the case of arginase and urease. Both of these enzymes in impure preparations are inactivated with more or less rapidity by exposure to oxygen, but when purified the inhibiting action is much less.[80,81,93,116,146] In purification, the removal of catalytic amounts of heavy metals—which may catalyze the oxidative inactivation of enzymes—must be borne in mind as a possible cause for their increased resistance.

Gale[87] found that formic dehydrogenase from *B. coli* was inactivated by oxygen. The inactivation was shown not to be due to the production of H_2O_2, oxalic acid or formaldehyde.

Lehman[119] studied the effect of oxygen pressures and pH upon succino-oxidase activity. In general maximum activity was found at comparatively very low oxygen tension, varying somewhat with pH but averaging 49 to 50 mm. Hg. At higher tensions the activity decreased. Bohr and Bean[45] found that preliminary exposure of succino-oxidase from pig heart to oxygen at 5 to 7 atmospheres decreased the subsequently measured activity (as measured by the Thunberg method) from 10 to 50%. No restoration of activity occurred after standing in air. In connection with these examples of the inactivating action of oxygen upon enzymes, attention is called to the point made by Brooks[52] that oxygen may be both inhibitor and reactor; in certain inorganic as well as biochemical reactions it is known to play this dual rôle.

In the following discussion of hypotheses of the toxic effect of oxygen upon enzymatic action, the names given to the hypotheses are those of the Reviewers. In most cases the original work was not done as a primary study of oxygen poisoning. The Reviewers have placed their own interpretation upon the experimental data, but have been careful to distinguish in their discussion their own from the original authors' opinions.

The "Active Oxygen" Hypothesis. Libbrecht and Massart[121] reported studies on succino-dehydrogenase. They constructed a pressure chamber to contain a manometric apparatus of the Warburg type. Small motors in the pressure chamber controlled from the outside manipulated the apparatus. To prevent burning out of the motors, the chamber was filled with air or nitrogen at high pressure, but the respiratory vessels proper, being connected to small balloons containing oxygen, were filled at high pressures (5 atmospheres) upon elevation of the pressure in the chamber. In the case of a freshly prepared succino-oxidase system, the authors found that 5 atmospheres of oxygen completely stopped oxygen uptake in the presence of succinate. That the true dehydrogenase activity was blocked was shown by the fact that the further addition of methylene blue did not restore oxygen uptake. However, aged preparations, or those treated with cyanide to inactivate the cytochrome oxidase system, were unaffected by high oxygen pressure since with succinate such preparations took up oxygen actively provided methylene blue was added to replace the lost cytochrome system as oxygen acceptor. From these

observations, Libbrecht and Massart concluded that molecular oxygen *per se* is non-toxic but that the cytochrome oxidase system together with high oxygen inactivates irreversibly the succino-dehydrogenase by "l'oxygène actif." The term "l'oxygène actif" is too vague a conception for current acceptance. Perhaps the hypothesis could be re-framed by stating that the cytochrome system together with oxygen at high pressures oxidizes the succino-dehydrogenase to an inactive form. This unique hypothesis of oxygen poisoning receives no support from the experimental work of Stadie and associates.[161]

Hypothesis of Reversible Oxidation of Ferrohemochromogens. This well-substantiated and interesting hypothesis of oxygen poisoning centers around the enzyme, hydrogenase.

Hydrogenase catalyzes the exchange reactions:

$$\tfrac{1}{2}H_2 = H^+ + E$$
$$2H_2 + O_2 = 2H_2O$$
$$H_2 + CO_2 = HCOOH$$
$$H_2 + X = H_2X$$

It is present in a variety of bacteria and algæ, but not in mammalian tissue. Stephenson and Stickland,[162] who first described the enzyme, observed that it was inactivated by molecular oxygen, as did Wieland and Pistor,[169] Claren,[71] and Gaffron.[86] Wilson, Lee and Wilson[171] studying the hydrogenase activity of azotobacter revealed a miniature picture of the oxygen problem in mammals. As the oxygen tension rose from low levels the activity of the hydrogenase system increased rapidly since oxygen was playing the essential rôle of reactant. But an optimal oxygen tension was soon attained beyond which a toxic zone was reached wherein activity diminished and finally ceased.

It is upon the interesting and important experiments of Hoberman and Rittenberg[102] that the hypothesis under discussion is based. Using deuterium to measure the activity of the hydrogenase from *proteus vulgaris* they found that the inactivation by oxygen was completely reversible. Reversal could be brought about slowly by re-equilibration with deuterium, and rapidly by reducing agents (hydrosulfite), or biologic agents such as glucose, pyruvate, succinate, formate, or fumarate. The authors concluded that hydrogenase is an iron hemochromogen which can exist in either the reduced or oxidized state. Oxygen inactivation is due to the formation of inactive ferrihemochromogen; reversal of inactivation is brought about by reduction to the active ferrohemochromogen; rapidly by reducing agents, and slowly by deuterium. In further support of this conclusion is the fact that cyanide inactivates under aërobic but not under anaërobic conditions. This was attributed by the authors to the well-known fact, as in the case of peroxidase and catalase, that reduced iron hemochromogens do not combine with cyanide. This attractive and well-substantiated hypothesis of the mechanism of oxygen inactivation of an enzyme cannot, however, explain all toxic action of oxygen. It is even impossible to conclude that all iron or metallo-hemochromogens will react similarly, since in unpublished experiments Stadie, Riggs and Haugaard[161] have found that catalase, a hemochromogen enzyme, is resistant to prolonged action of oxygen at high pressures.

Hypothesis of Action of Oxygen upon Co-enzymes: Glyoxalase. This enzyme catalyzes the dismutation of methyl glyoxal to lactic acid and is abundantly present in mammalian tissue. Reduced glutathione functioning as a co-enzyme is necessary for its action. Jowett and Quastel[110,111]

showed for the glyoxylase of human red cells and rat tissues a progressive inhibition of enzymatic activity in the presence of oxygen which they attributed to the formation of the inactive oxidized form of glutathione.

This appears to be the only known instance of an enzyme system inhibited by the action of oxygen upon the co-enzyme. However, the case of cysteine and carboxypeptidases studied by Irving, Fruton and Bergmann[106] (see *infra* under Formation of Enzyme Inhibitor by Molecular Oxygen for discussion) is also properly discussed here. Cysteine, according to these authors, forms a complex with the enzyme which thereupon acquires activity. The oxidation of the cysteine by molecular oxygen to cystine results in inactivation.

Hypothesis of Inactivation by Oxidation of Activating Metal in Enzyme. This possibility is illustrated by the studies of Warburg and Christian on yeast zymohexase.[167] The enzyme is an important one in carbohydrate metabolism since it catalyzes the splitting of hexose diphosphate into 2 molecules of triose phosphate. The enzyme requires free reduced Fe, Cu, or Co for activation. The action of oxygen is through cysteine in the following way: in the presence of a small amount of cysteine molecular oxygen oxidizes the metal, in which state it is no longer activating. In the case of zinc, which also activates the enzyme, but exists only in one valence state, oxygen and traces of cysteine are without influence. A second mechanism of inactivation by cysteine must be mentioned although not related to oxygen action: an excess of cysteine either anaërobically or aërobically inactivates because of complex formation removing the activating metal.

However, the possibility is remote that this particular mechanism of oxygen action on important carbohydrate metabolic processes is a factor in oxygen poisoning in mammalian organisms, since the zymohexase prepared from muscle is completely independent of metals for activity and in consequence cysteine and oxygen are without influence upon its activity. However, as a prototype, similar oxygen-enzyme interaction may exist in mammalian tissue although the Reviewers have found no references to such.

Formation of Enzyme Inhibitor by Molecular Oxygen. An interesting form of oxygen inactivation is that discussed by Irving, Fruton and Bergmann[107] in the case of swine kidney and beef spleen carboxypeptidases. Experimentally they used the dipeptide carbobenzoxyglycylphenylalanine as substrate and studied its rate of hydrolysis. Cysteine is required for the activation of these enzymes. Oxygen may inactivate by oxidizing the cysteine to cystine which no longer activates (*v. supra*), similar to the case of glyoxalase. But another type of inactivation may result by the action of molecular oxygen, according to the authors. In the first case, if the enzyme was preliminarily equilibrated in the presence of oxygen with cysteine before the addition of the substrate, a diminished but constant reaction rate was obtained. In the second case, if the preliminary equilibration period was omitted, the aërobic digestion began at almost as high a rate as the anaërobic digestion, but this rate diminished to the same low but constant rate as that observed in the first case. This inhibition, the authors concluded, was not due to oxidation of cysteine, which was present in excess and remained essentially unchanged, but cysteine reacted in the course of the incubation with an unknown component of the crude swine kidney extract to form an inhibitor for the carboxypeptidase. Swine kidney pepsinase which requires no activator (*i. e.*, cysteine) was not inactivated by oxygen. These experiments not only illustrate an interesting possible mechanism of oxygen inhibition of enzymatic systems,

but also show that a sulfhydryl activator such as cysteine may react in two ways with molecular oxygen to influence enzyme action: (1) by being itself oxidized and thus losing its function as an activator; and (2) by reacting together with precursors to produce enzyme inhibitors.

Action of Oxygen Upon the Sulfhydryl Enzymes. Recently there has been a renewed interest in the so-called sulfhydryl enzymes. These enzymes are assumed to be active or inactive depending upon the state of the sulfur as a constituent part of the enzyme molecule. Two possibilities are recognized: (1) The sulfur exists in the reduced or sulfhydryl form, designated commonly as EnSH. In most cases (insulin is an exception) the enzyme is active in this state, hence the term, sulfhydryl enzymes. (2) The enzyme may contain the sulfur in the oxidized or dithio form, usually designated by the symbol EnS:SEn, in which condition (excepting insulin) the enzyme is inactive. The transformation of one state to another is in most cases reversible and may be brought about on the one hand by oxidizing agents such as porphyrindine, iodine, iodosobenzoate, oxidized glutathione, iodoacetamide, and so forth, or, on the other hand, by reducing agents such as cysteine, reduced glutathione, thioglycollic acid, hydrosulfite, HCN, H_2S, etc. Reversible inactivation may also be brought about by the use of certain mercaptan reagents, *viz.:* cuprous oxide, mercurials such as chloromercuribenzoic acid, and organic arsenicals which presumably react with the $-SH$ group producing mercaptides according to the equation: $EnSH + X = EnS{\cdot}X$.

The possibility that oxygen at ordinary or high pressures acts as the oxidizing agent to produce enzymatic inhibitions by this mechanism is obviously real, and indeed there is experimental evidence in the case of succino-oxidase that such is the case. This hypothesis, therefore, becomes important in the discussion of the mechanisms of oxygen poisoning.

For discussion of the literature on the sulfhydryl enzymes, reference is made to the review article of Hellerman[92] and the recent articles of Barron and Singer[16] and Potter and DuBois.[141] Only that portion which is pertinent to the subject of oxygen poisoning will be discussed here.

Hellerman[92] reported that urease and arginase—two sulfhydryl enzymes —are inactivated by oxygen but the inactivating action of oxygen is less on the purified enzyme presumably because catalytic copper was removed. Since succino-dehydrogenase is the best studied enzyme in relation to oxygen effects, a more extended discussion is in order. Hopkins and Morgan[104] showed that succino-dehydrogenase, whose action is independent of a co-enzyme, is completely inactivated by the addition of oxidized glutathione. Upon further addition of reduced glutathione or cysteine, complete reactivation is observed. Hence, they concluded that succino-dehydrogenase is a sulfhydryl enzyme and that activity is dependent upon the reduced form—EnSH. In later studies, Hopkins *et al.*[105] made the important observation that malonic, fumaric and succinic acids protected the enzyme from the oxidizing action of the glutathione. Potter and DuBois[141] studied in detail the mechanism of the catalytic action of succino-dehydrogenase. They agreed with Hopkins and Morgan that the action is dependent upon the presence of the $-SH$ groups as constituent parts of the enzyme molecule. They picture the enzyme as being in an equilibrium state between oxidized and reduced form, *viz.:* $EnSH \rightleftarrows EnS + H$.

Alternate oxidation by the cytochrome oxidase system and reduction by substrate explains the mechanism for the oxidation of succinic acid. They further suppose that the active $-SH$ groups are situated between two "affinity" points which combine with the two carbonyl groups of

the succinic acid to hold it for the duration of the action of the oxidative process. Malonic acid also combines with these two points and "covers" the active center —SH group, thus protecting it from the oxidative action of oxidized glutathione or other oxidizing agents. The inactivating action of high pressure oxygen upon succinodehydrogenase has already been discussed. That the mechanism of inactivation is similar to that of glutathione is indicated by the fact that the oxygen inactivation is reversible in part by reduced glutathione, but more significantly by the fact that malonate protects completely.[161]

Whether the inactivating action of high oxygen by this mechanism is a universal manifestation with sulfhydryl enzymes remains to be determined by further experimentation.

Oxidation-reduction Potential of Environment on Enzyme Activity. That enzyme activity may be influenced by non-specific effects such as change of the oxidation-reduction potential of the medium is indicated in the recent work of Sizer and Tytell,[156] and Sizer.[155] They altered the oxidation-reduction potential of their media by the use of a variety of poisoning agents over a wide range and found that the activity of crystalline urease and yeast invertase was a continuous function of the potential. Urease showed a maximum activity at +0.15 volt; invertase showed a constant activity from −0.27 to +0.60 volt, above which it fell off sharply.

Whether or not the oxidation-reduction potential of mammalian tissue can be altered by high pressures of oxygen is unknown; but the possibility that such a mechanism may be operative in oxygen poisoning is mentioned for the sake of completeness.

Summarizing the data on enzymatic systems, the likelihood is increasing that the toxic action of high pressures of oxygen will be explained in the light of inhibitory actions on enzymes with resultant severe disturbances of essential metabolic cellular reaction. The evidence in the literature is scanty and non-systematized, but is sufficient to suggest the following possible modes of action of oxygen: (1) Oxidation of a co-enzyme to the inactive oxidized form. (2) Oxidizing activating sulfhydryl compound. (3) Oxidizing active —SH groups of enzyme molecule proper. (4) Oxidation of metallo-hemochromogen to inactive oxidized form. (5) Oxidizing activating metal constituent. (6) Formation of inhibitor from precursor other than the enzyme. (7) Inhibition of enzymatic activity by changing oxidation-reduction potentials of medium.

Summary. The literature on the subject of oxygen poisoning is reviewed under the following headings: (1) Symptomatology, (2) Pathologic Anatomy, (3) Blood, (4) Circulation and Peripheral Vessels, (5) Metabolism, (6) Blood Gas Equilibrium, (7) Influencing Factors, (8) Tolerance, Adaptation and Oxygen Therapy, (9) Oxygen Aero-embolism from Rapid Decompression, (10) Isolated Surviving Tissue, (11) Neoplasia, (12) Microörganisms, (13) Dual Function of Hemoglobin, and (14) Enzymatic Systems.

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PATHOPHYSIOLOGY AND TREATMENT OF DCS

Articles selected by John M. Hallenbeck, M.D.
Naval Medical Research Institute
National Naval Medical Center

15

THE PATHOPHYSIOLOGY AND TREATMENT OF DECOMPRESSION SICKNESS

J. M. HALLENBECK

It is fitting that the first reference should be by Bert (1878) since this work is the apotheosis of a seminal document. An astonishing number of principles are elucidated in this work, such as individual and interspecies variability in susceptibility to decompression sickness and temporal variability in susceptibility to decompression sickness within an individual. The fundamental cause of decompression sickness was correctly attributed to formation of inert gas bubbles in the organism according to Dalton's law. Furthermore, the ability of intravascular gas to interfere with circulation, and of interstitial and intracellular gas to distort and disrupt tissue was appreciated. The prophylactic value of controlled decompression was described and the principle of recompression therapy breathing oxygen was proposed and its value documented. A later article by Boycott et al. (1908) continues the story. This treatise, describing principles of uptake and elimination of inert gas, represents a pioneering effort to develop principles for the design of safe decompression tables. It also describes experiments in goats in which white matter infarcts were observed in the spinal cord after decompression-producing dives.

A. R. Behnke is a central figure in virtually all aspects of underwater physiology, and his articles (Behnke et al., 1936, 1937) provide the rational underpinning for use of hyperbaric oxygen in the treatment of decompression sickness. In addition, manifestations of decompression sickness in the dog were graphically described, the tendency for a "double-dive" to produce spinal cord damage in air-breathing animals was noted, and oxygen unsaturation of arterial blood during decompression sickness was documented. A great deal of clever and incisive research into the pathophysiology of decompression sickness was carried out at the Naval Medical Research Institute during and after World War II. An account of this work as well as that performed in other laboratories appears in Catchpole and Gersh (1947). This is a comprehensive discussion of the pathophysiology of decompression sickness. The possibility of extravascular bubbles during decompression from high atmospheric pressures, primarily in lipid-rich structures, was cited. An account of the first of the current generation of air treatment tables is presented by Van Der Aue et al (1947).

Many aspects of neuropathology bear the personal stamp of Webb Haymaker, and nervous system involvement in decompression is no exception, as attested by his monumental work (Haymaker, 1957). This chapter discusses the pathogenesis of spinal cord damage in decompression sickness and postulates that arteriolar gas bubble embolization of the spinal cord, acting in concert with embarrassment of spino-vertebral venous circulation, is responsible for the lesions. It is an exhaustive account of the pathophysiology and pathophysiologic mechanisms in decompression sickness and air embolism, and is "must" reading for any serious student of these disorders.

Several milestone articles deal with a single aspect of decompression sickness. One article by Cockett et al. (1965) is an early publication describing the importance of plasma volume loss in decompression sickness. The minimal recompression, hyperbaric oxygen treatment tables owe their existence to the studies of Workman and colleagues (1969). This important paper describes the rationale and application of tables that are now in use throughout the world. The hyperbaric oxygen schedules are compared with the results of USN tables 3 and 4, and are found superior. Another paper by Chryssanthou et al. (1970) highlights an aspect of decompression sickness; it implicates vasoactive substances in the pathogenesis of decompression sickness. The flow of blood, a non-Newtonian fluid, in the microcirculation is governed by complex principles and can undergo major deviations from normal during decompression sickness. The article by Wells et al. (1971) documents the disturbance of rheology in decompression sickness. An early paper in a series implicating obstruction of the epidural vertebral venous system as an important pathogenetic mechanism underlying spinal cord damage in decompression sickness is provided by Hallenbeck et al. (1975). A final article in this chronological sequence by Philp (1974) is a review of blood changes associated with decompression sickness by a leading investigator in the field and contains most of the important references.

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J. M. HALLENBECK

The articles included in this section are reprinted by permission of their original publishers as follows:

Behnke A. R., Shaw L. A., Messer A. C., Thomson R. M., Motley E. P.: The circulatory and respiratory disturbances of acute compressed-air illness and the administration of oxygen as a therapeutic measure. *Am J Physiol* 1936; 114:526–533. Copyright 1936, American Physiological Soc.

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THE CIRCULATORY AND RESPIRATORY DISTURBANCES OF ACUTE COMPRESSED-AIR ILLNESS AND THE ADMINISTRATION OF OXYGEN AS A THERAPEUTIC MEASURE[1]

ALBERT R. BEHNKE,[2] LOUIS A. SHAW, ANNE C. MESSER, ROBERT M. THOMSON AND E. PREBLE MOTLEY

From the Department of Physiology, Harvard School of Public Health, Boston, Mass.

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Heller, Mager and von Schrötter (1900) found that rapid decompression of dogs from pressures of 60 to 70 pounds above atmospheric caused intravascular bubble formation which produced asphyxia by occlusion of the pulmonary capillary bed, and frequently paralysis of the hind extremities through a deprivation of the blood supply to the spinal cord. The object of the present investigation is to obtain further information regarding the causes of acute compressed-air illness and to ascertain the value of oxygen inhalation as a therapeutic measure.

The treatment of compressed-air illness in standard practice calls for recompression. Since the volume of an air embolus is inversely proportional to the barometric pressure upon it, recompression will reduce the size of the embolus and give relief to the characteristic symptoms. But unless the emboli are absorbed, then, when the pressure is again brought to normal, they will expand again and the symptoms will return. If time be permitted, air emboli will ultimately be absorbed and dissipated because the partial pressure of the nitrogen in them is higher than that of the nitrogen in the blood and body fluids, thus establishing a diffusion pressure head. The rate at which the absorption takes place is proportional to this pressure head.

In treating the compressed-air illness which was deliberately induced in our experiments, the dogs were recompressed at 30-pound gauge pressure, during which procedure some of the animals breathed air, while others breathed oxygen. When oxygen is breathed, the partial pressure of nitrogen in the arterial blood instantly becomes 0, and must approach 0 in the venous blood and tissues. As a result, the effective pressure head of the nitrogen in the embolus is much greater than when air is breathed. By a simple calculation, which cannot be discussed here, we have estimated that when air is breathed under a pressure of 30 pounds the partial

[1] This research was aided by the Miriam Smith Rand Fund.

[2] Member of the United States Naval Medical Corps.

pressure of nitrogen in an air embolus is about 2144 mm., and in the arterial blood about 1773 mm., so that the nitrogen in an embolus has a pressure head of 2144 − 1773 = 371 mm. On the other hand, when oxygen is breathed this pressure head is 2144 − 0 = 2144 mm. Thus, under these conditions, oxygen inhalation should cause the absorption of air bubbles about 5.8 times as rapidly as air. Based upon such considerations, oxygen was administered in some of the experiments to ascertain its possible advantages in relieving the symptoms under investigation.

METHOD. Dogs were anesthetized with Dial.[3] One femoral artery was cannulated and connected to a manometer to record blood pressure. Samples of arterial blood were obtained from the other femoral artery. Samples of mixed venous blood were taken by means of a sound inserted through the external jugular vein into the right heart. Records were made of the respiratory rate, pulse rate, and arterial blood pressure. The oxygen saturation of the arterial and mixed venous blood was determined by equilibrating with air containing 25 per cent oxygen. When pure oxygen is breathed at a pressure of 30 pounds the capacity of the blood to hold oxygen is increased by approximately 4.2 volumes per cent, this being the amount taken up into physical solution. The carbon dioxide tension of the blood was determined by correlating the carbon dioxide content with the carbon dioxide dissociation curve. Bubble formation was observed macroscopically in the blood vessels of the living animal by a skin incision in the medial aspect of the thigh, and at death by autopsy.

The experiments were done in a pressure chamber large enough to accommodate the operators as well as the dog. The experimental procedure may, for convenience, be divided into 5 periods, and may be described in order of their sequence: 1. The control period, during which the dog breathed air at normal pressure and control records were made. 2. The compression period, during which the dog was subjected to air at 65-pound gauge pressure for 105 minutes. The pressure was then dropped to normal in 5 or 6 seconds. 3. The period which followed rapid decompression, during which the dog breathed normal air at normal pressure and the symptoms of compressed-air illness became apparent. Owing to the asphyxial character of these symptoms, which will be described later, this period is designated as the asphyxial period. 4. The recompression period, during which the pressure was raised to 30-pound gauge for 84 minutes followed by stage decompression for 30 minutes until the pressure was again normal. In some experiments air was breathed during this period, and in others oxygen was inhaled, in order to determine

[3] The authors wish to thank Dr. Charles C. Haskell of the Ciba Company, New York City, for his kindness in furnishing the dial-urethane solution used as the anesthetic in these experiments.

whether or not oxygen is more efficacious than air in dissipating air emboli. 5. The recovery period which followed recompression, and during which the dog breathed air at normal pressure. During this period the effects of oxygen inhalation, if any, were made apparent. Except in period 2, when the pressure was at 65 pounds, the operators were in the chamber with the dog.

TABLE 1

The blood pressure, respiratory rate and autopsy findings in dogs suffering from acute compressed-air illness

EXPERIMENT	BLOOD PRESSURE (MM. Hg)				RESPIRATORY RATE				AUTOPSY
	Control	Asphyxial period*	Recompression	Recovery†	Control	Asphyxial period*	Recompression	Recovery†	
Air inhalation									
2	147	80	108	82	15	28	8	10	Bubbles in right ventricle and in all blood vessels
4	97	68	70	84	30	62	20	40	Bubbles in all blood vessels
5	142	78	122	80	14	84	14	70	Bubbles in all blood vessels
6	115	54	100	100	26	100	20	80	Bubbles in all blood vessels
9	132	80	90	114	20	134	32	140	Bubbles in all blood vessels
12	146	64	118	100	30	84	56	86	Bubbles in right and left ventricles and in all blood vessels
Oxygen inhalation									
3	117	60	115		22	92	20		Bubbles in peripheral veins only
11	158	84	94	62	20	64	20	34	Bubbles in peripheral veins only
8	118	30	92	100	10	58	22	30	No bubbles
10	140	70	94	80					Bubbles in peripheral veins only
1	124	84	106	120	22	100	20	44	

* Data for asphyxial period taken just prior to recompression.

† Data for recovery period taken after breathing normal air for 1 hour.

EXPERIMENTAL RESULTS. The data on blood pressure, respiratory rate, and autopsy findings are given in table 1, and the data relative to the blood gases in table 2.

Asphyxial period. During the period which followed instantaneous decompression from a pressure of 65 pounds to atmospheric, and designated as the asphyxial period, the blood pressure at first rose sharply and then steadily fell. The duration of this period varied in different animals from 9 to 43 minutes, depending upon the rate at which the blood pressure fell. It was necessary in all cases to raise the barometric pressure again

TABLE 2

The oxygenation and the carbon dioxide tension of the blood of dogs suffering from acute compressed-air illness

EXPERIMENT	PERIOD*	OXYGEN CONTENT		ARTERIAL-VENOUS DIFFERENCE	OXYGEN CAPACITY	PER CENT OXYGEN SATURATION		PRESSURE CARBON DIOXIDE IN ARTERIAL BLOOD
		Arterial	Venous			Arterial	Venous	
		volumes per cent						*mm. Hg*
Air inhalation during recompression								
6	Control		7.3		15.7			
	Asphyxial	6.8						
	Recompression	17.8	12.0	5.8				
	Recovery	10.5						
7	Control	19.3	15.2	4.1	22.4	86	68	
	Asphyxial	18.4	8.7	9.7				
	Recompression	25.8	11.5	14.3				
	Recovery	24.3	8.8	15.5	29.0	84	30	
9	Control	15.9	10.1	5.8	17.7	90	57	45.0
	Asphyxial	5.4	0.5	4.9	22.4	24	2	59.0
	Recompression	17.9	7.9	10.0	20.3	88	39	
	Recovery	5.9	2.3	3.6	22.8	26	10	
12	Control	14.6	12.0	2.6	15.9	92	75	38.0
	Asphyxial	6.9	2.8	4.1	18.7	37	15	51.0
	Recompression	16.0	11.3	4.7	16.8	95	70	
	Recovery	Death						
Oxygen inhalation during recompression								
8	Control	20.9	16.7	4.2	23.1	91	72	37.0
	Asphyxial	23.5	17.1	6.4	26.7	88	64	46.0
	Recompression		20.5					
	Recovery	26.7	16.9	9.8	28.5	94	59	
10	Control	20.6	17.0	3.6	22.8	90	75	
	Asphyxial	14.6	7.7	6.9	26.1	56	30	
	Recompression	31.7	20.0	11.7	31.5†	100	64	
	Recovery	26.9	7.3	19.6	29.8	90	24	
11	Control	19.3	14.6	4.7	22.2	87	66	50.0
	Asphyxial	18.3	10.7	7.6	26.7	70	40	60.0
	Recompression	29.0	15.9	12.1	29.6†	95	54	
	Recovery	22.0	11.4	10.6	24.5	90	47	

* Data for asphyxial period taken just prior to recompression. Data for recovery period taken after breathing normal air for 1 hour.

† Four and two-tenths volumes per cent added to normal capacity by oxygen in physical solution.

to prevent death from circulatory failure. The falling blood pressure was accompanied by an accelerated respiratory rate, which increased from an average control value of 21 to 81. The pulse rate fell from an average of 138 to 94.

In every case, with the exception of experiment 8, the oxygen saturation of the arterial blood fell below 70 per cent, and in experiment 9 fell to 24 per cent. The deficient oxygenation of the arterial blood was accompanied by a rise in the arterial carbon dioxide tension. There was a marked increase in the arterial-venous oxygen difference, indicating a reduced circulation rate. Bubbles were frequently present in the blood samples drawn from the femoral artery and from the right heart. Small bubbles were seen in all cases circulating through the cutaneous arteries and veins which had been exposed by an incision in the thigh.

The picture here presented is one of acute anoxemia, caused by the formation of air bubbles throughout the entire vascular system, sufficient in volume to interrupt the continuity of the blood stream.

Recompression. During recompression at 30 pounds, or 3 atmospheres absolute, the volume of the bubbles is reduced to one-third of that existing at 1 atmosphere of pressure. The blood pressure improved but never returned to its control value, the average value of the latter being 130 mm. Hg as compared with 101 mm. under recompression; the respiratory rate decreased to the initial level; and the arterial blood became normally saturated. The arterial-venous oxygen difference, on the other hand, remained high. The beneficial effects of oxygen inhalation as compared with air in promoting the absorption of bubbles were not apparent during this period. The continued low blood pressure, notwithstanding a reduction of the nitrogen emboli to one-third of their initial volume, suggests a more or less sustained impairment of the vascular system caused by the profuse evolution of nitrogen into the blood stream which took place during the asphyxial period.

Recovery. It was found that the lowered blood pressure and increased arterial-venous oxygen difference which had failed to return to normal during recompression remained abnormal during the recovery period, irrespective of whether air or oxygen at 1 atmosphere was breathed. The respiratory rate of the dogs that breathed oxygen during the recompression period was much lower during the recovery period than that of the dogs which breathed air, the average values being 36 for the former as compared with 71 for the latter. The oxygen saturation of the arterial blood of the dogs which had previously breathed oxygen was normal during the recovery period, whereas the oxygen unsaturation of the dogs which had breathed air was very marked. Although figures for the per cent saturation are lacking in experiment 6, an oxygen content of only 10.5 volumes per cent indicates a very low saturation value. In experiment 7, the saturation was 84 per cent and in experiment 9, 26 per cent. In

experiment 12 the dog died soon after the pressure reached normal, but the dark color of the arterial blood left no doubt as to its oxygen unsaturation.

Autopsy. At autopsy it was found that the dogs which had previously breathed oxygen suffered from nitrogen emboli only to a minor degree, the only bubbles observed being confined to the peripheral vessels. The larger vessels and heart chambers were wholly free from bubbles. The presence of bubbles in the peripheral vessels may be due to the fact that the blood pressure was too depressed to overcome the inertia and force them into the general circulation where they would be absorbed. On the other hand, when the dogs had breathed air during recompression, not only were bubbles seen in the peripheral vessels but also in the venae cavae, the larger arteries and in both chambers of the heart. The right ventricle was frequently dilated and filled with a gas-blood emulsion and bubbles were present in the coronary arteries.

Discussion. Binger, Brow and Branch (1924) showed that when multiple emboli of the pulmonary vessels were produced in dogs experimentally by the intravenous injection of seeds of various sizes, rapid breathing and arterial anoxemia resulted. The rapid breathing was proved to be the result of anoxemia. With relief of anoxemia by oxygen inhalation rapid breathing ceased. The partial blockage of the pulmonary capillary bed by nitrogen emboli causes the blood to be shunted through that part of the route which offers the least resistance to blood flow. Binger, Brow and Branch found that, notwithstanding the reduction in the functional capillary bed of the lungs following embolic obstruction, the cardiac output per minute was only 14 per cent less than normal. They concluded that this was made possible by a dilatation of the intact route, accompanied by an increased pulmonary blood pressure. The normal saturation of the hemoglobin with oxygen is, therefore, obstructed in a twofold manner: 1, the increased rate of flow through the intact capillaries does not permit sufficient time for the blood to assume its normal load of oxygen; and 2, the dilated capillaries are crowded with corpuscles in columns so thick as to interfere with the normal inward diffusion of oxygen. Rapid breathing follows as a natural consequence of the anoxemia. The increase in the carbon dioxide content of the arterial blood is insignificant and by no means comparable to the oxygen unsaturation. Binger, Brow and Branch attribute this to the fact that the solubility of carbon dioxide is very much greater than that of oxygen.

The symptoms which follow the obstruction of the pulmonary circulation by the intravenous injection of particulate matter are so similar to the symptoms observed in acute compressed-air illness as to leave little doubt of the cause of anoxemia which follows rapid decompression from high air pressures.

In the experiments of Binger, Brow and Branch the blood pressure was

unaffected by pulmonary embolism, whereas in our own experiments the blood pressure fell and never returned to normal, even after the emboli had been apparently absorbed, or at least reduced to insignificant proportions. This difference in the reactions produced may be caused by a difference in the distribution of the emboli. Emboli produced by intravenous injection stop in the lungs and probably do not pass through into the general circulation, so that obstruction is confined to the pulmonary vessels only. On the other hand, air emboli produced by decompression are formed in the blood stream of the body as a whole and may, therefore, cause impairment of the bodily functions by interfering with the blood supply to the nervous tissues. Such impairment of the nervous tissue controlling the circulation may account for the depressed blood pressure associated with profuse air emboli caused by rapid decompression.

That the damage done to the nervous system persists even after the cause has been removed is indicated by the fact that the blood pressure, which is depressed while the barometric pressure is at 3 atmospheres absolute (30 lb.), remains unaffected when the barometric pressure drops to 1 atmosphere again. If the depressed blood pressure, existing under a pressure of 3 atmospheres, was caused by residual bubbles which failed to be absorbed, then, at 1 atmosphere of pressure, the bubbles should expand to 3 times their former size and the resultant injury to the nervous tissue should be increased proportionately. This, however, is not the case.

Further evidence of the injury to the nervous system, caused by emboli formed within the body, is afforded by experiments done in this laboratory upon intact unanesthetized dogs, which have been subjected to conditions of pressure and treatment identical with those described in this paper. These animals, after being released from compression, become paralyzed in the hind legs, and fail to recover even after a period of days. The paralysis which is manifest in the intact animals but obscured in those under anesthesia, leaves no doubt of the injury done to the nervous tissue.

Owing to the toxic effects of breathing oxygen under pressure the time of exposure is limited. It has been shown by Behnke, Forbes and Motley (1935) that pure oxygen under a gauge pressure of 30 pounds can be tolerated for about 3 hours before the toxic effects are manifested by contraction of the visual field, rise in blood pressure and increase in pulse rate. Behnke, Johnson, Poppen and Motley (1935) have shown that when the oxygen pressure is increased to 45 pounds syncope or a convulsive seizure may occur. It would, therefore, be wise to limit the pressure of the oxygen breathed to 30 pounds. At this pressure there can be little doubt that all, or nearly all, the nitrogen bubbles will be absorbed in severe cases of compressed-air illness.

SUMMARY

1. Nitrogen emboli were produced in the blood of anesthetized dogs by rapid decompression from air compressed to 65 pound gauge pressure for 105 minutes. The condition thus produced was similar to that of acute compressed-air illness.

2. The characteristic symptoms observed were rapid breathing, temporary rise followed by a fall in blood pressure, a retarded pulse rate, oxygen unsaturation of the arterial blood and a marked increase in the arterial-venous difference.

3. The rapid breathing and oxygen unsaturation of the arterial blood are attributed to embolic blockage of the pulmonary circulation.

4. The fall in blood pressure and increased arterial-venous difference is attributed to embolic injury to the nerve tissue which controls circulation.

5. In order to dissipate the emboli the dogs were recompressed to 30-pound gauge pressure. During this time some of the dogs breathed air and others pure oxygen, to test the efficacy of oxygen therapy in the treatment of compressed-air illness.

6. When the pressure again returned to normal it was observed that when oxygen was breathed, the oxygen unsaturation of the arterial blood was relieved, the respiratory rate returned to a normal value and only a few bubbles remained at autopsy. When air was breathed during recompression, a return to normal pressure caused the reformation of bubbles as observed at autopsy, and a return of the rapid breathing and oxygen unsaturation of the arterial blood.

7. The experimental results justify the use of oxygen to accelerate the absorption of nitrogen emboli.

The authors wish to acknowledge their indebtedness to The Linde Air Products Company, New York City, for the oxygen used in these experiments.

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BAROMETRIC PRESSURE

Researches In Experimental Physiology

BY

PAUL BERT

Translated from the French by

MARY ALICE HITCHCOCK, M.A.

Formerly Professor of Romance Languages at the University of Akron

and

FRED A. HITCHCOCK, Ph.D.

Associate Professor of Physiology at The Ohio State University

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Subchapter III

EFFECT OF SUDDEN DECREASE OF PRESSURE BEGINNING WITH SEVERAL ATMOSPHERES

The subject of our researches here becomes much more interesting. Indeed, it draws nearer the phenomena which we mentioned in the historical part, in speaking of laborers who work on the piers of bridges and of divers in suits.

I shall begin, as usual, by a detailed account of a certain number of experiments. I report first those in which the decompression was made without interruption and as rapidly as possible.

1. Decompression without Interruption.

A. Experiments Made on Sparrows.

Experiment DV. July 20. House sparrow. Seltzer water receiver. Brought in 20 minutes to 8 atmospheres; left for 5 minutes under pressure. Opened the large cock first, and made the decompression in a few seconds. *Struggled at the moment of decompression,* then did not appear sick, and survived.

Experiment DVI. August 3. House sparrow. Same apparatus. Taken to 8 atmospheres at 12:30.

At 2 o'clock, sick; at 2:45, very sick. Took a sample of air which contained 2.1% of CO_2. Tension: $2.1 \times 8 = 16.8$.

Opened the large cock suddenly; the bird fell backward violently; rose immediately: its rectal temperature was 25°, that of the outer air being 20°, blood of the jugular veins very red; no gas seen. Remained on its back and died in 10 minutes. At death, the venous blood is dark; bubbles of gas seen in the jugulars.

Experiment DVII. May 1. House sparrow. Glass cylindrical receiver

2:05, raised to 10 atmospheres; surrounded by papers wet in potash solution so that the CO_2 is absorbed as it is produced.

At 3:40, the bird appears dead; the pressure is 9½ atmospheres; the air contains 14.1% of oxygen, and no doubt very little carbonic acid. Decompression made rapidly. Almost immediately, the bird, which raised its head at the moment when the cock was opened, became very lively; bloody suffusions on the cranium. Survived.

Experiment DVIII. May 10. House sparrow. Cylindrical apparatus.

From 4:15 to 4:20, raised to 16 atmospheres. After 5 or 6 minutes shows quiverings with great distress, slight convulsions, etc. characteristic of poisoning by oxygen, the tension of which was $16 \times 20.9 = 334$. At 4:30, *decompression made in 1 minute; did not*

seem to suffer from the decompression; no gas in the jugulars, in which the blood was very red. Enormous bloody suffusions on the cranium. Rectal temperature 35°. At 4:35, great convulsions, died. Rectal temperature 34°. The blood was very red in the left heart, without gas. In the right heart and the jugulars, it was dark with gas in very small bubbles; these bubbles were present in the portal system.

Experiment DIX. October 27. Sparrow (cylindrical receiver). Taken to 8 atmospheres. Decompression made in 5 seconds. Taken from the apparatus, did not seem at all inconvenienced.

Experiment DX. October 27. Sparrow (cylindrical receiver). Taken to 10 atmospheres. Decompression made in 5 seconds. No symptom, survived.

Experiment DXI. October 27. Sparrow (cylindrical receiver.) Taken to 12 atmospheres. During this time remained motionless at the bottom of the apparatus. When sudden decompression was made, darted to the top of the cylinder, then fell back. Was dead before being taken from the apparatus. Air in quantity in the jugulars and the right heart.

Experiment DXII. October 27. Sparrow (cylindrical receiver). Taken to 14 atmospheres. Sudden decompression; died in a few minutes. Air in quantity in the jugulars and the right heart.

Experiment DXIII. October 27. Sparrow (cylindrical receiver.) Taken to 14 atmospheres. Sudden decompression, without symptoms. Found dead the next day.

Experiment DXIV. October 27. Sparrow; cylindrical apparatus. Taken to 15 atmospheres, and suddenly decompressed immediately. Removed from the apparatus, could not walk, flapped its wings, had convulsions, and soon died. Air in quantity in the jugular veins and the right heart.

Experiment DXV. June 29. Two sparrows were taken in one hour to a pressure of 7 atmospheres under a current of air maintained by the large sheet-iron cylinder. At this moment, the rubber communication tube burst; the decompression was instantaneous. The two birds died in a quarter of an hour.

We must add to these experiments made on sparrows the results of a great number of others already reported with another purpose in the subchapter of Chapter I. We shall return to them later.

For the moment I set aside the discussion which these experiments deserve and report those made on mammals.

First, rats, for which we generally used the small glass apparatuses.

B. Experiments Made on Rats.

Experiment DXVI. August 9, 1871. Rat. Seltzer water receiver.

9:25, placed at 7 atmospheres. 10:10, pressure fell to 6½; the animal is rolled up in a ball, with hair bristling; respiratory rate 75. I open the large cock suddenly; the animal arouses immediately, and does not seem to be in pain.

Experiment DXVII. August 10. Same animal, same apparatus.

4:10, placed at 6 atmospheres. 5:25, respirations difficult, dicrotic; the animal is lying curled up on the bottom of the vessel. Took sample of air, which contained 5.2% of CO_2. Tension: 5.2 x 6 = 31.2. The pressure then falls to 5½. I open the large cock suddenly. The animal almost immediately stands up on his feet, and seems quite well.

Experiment DXVIII. August 12. Same animal, same apparatus.

At 4:15, placed at 6½ atmospheres. The apparatus leaks; at 6 o'clock, the pressure is 4½ atmospheres; the animal is very sick. I take a sample of air, which contains 6.1% of CO_2.

Tension: 6.1 x 4.5 = 27.4. I open the cock wide; the rat does not recover immediately, but he is well the next day.

All the experiments reported next were made in the large cylinder of sheet-iron pictured in Figure 33. The large cock which is opened suddenly is the one lettered c:

Experiment DXIX. May 24. Two rats in the large cylindrical apparatus (experiment made before the Committee of the Institute).

They are taken to 8½ atmospheres; the decompression is made in 2 minutes. The rats run about when taken from the apparatus; a few minutes after, they become paralyzed and die. Gas is found in the whole venous system.

C. Experiments Made on Rabbits.

Experiment DXX. June 22. Rabbit.

Taken to 8 atmospheres. Decompressed in 3 minutes. Ears bright red; no symptom either immediate or later.

Experiment DXXI. November 7. Two rabbits.

Taken to 7 atmospheres. Decompressed in 2½ minutes. No symptoms.

Experiment DXXII. November 10. Same animals.

Taken to 8⅛ atmospheres; decompressed in 2¼ minutes.

No symptom either immediate or delayed.

Experiment DXXIII. November 15. Rabbit.

Taken to 6½ atmospheres. Decompressed in 4½ minutes. No effect.

D. Experiments Made on Cats.

Experiment DXXIV. May 23. Male cat, extraordinarily vigorous and wild. Taken to 10 atmospheres. Sudden decompression. Leaps

out of the apparatus, apparently well, and hides under a piece of furniture. Half an hour later, it is found there paraplegic. The hind legs are stiff, with the claws extruded; they are sensitive, as is the tail, but are no longer under voluntary control. Bloody urine containing spermatozoa is drawn from the animal. The anal sphincter is contracted.

May 24. Same condition; except that the tail and the hindquarters are entirely without sensitivity and are relaxed. By pinching a foot, very distinct reflex movements are obtained, which, however, do not pass from one member to the other.

The bladder is enormously distended by urine containing much blood.

The anal and vesical sphincters are strongly contracted.

The animal mews faintly; it is very weak, drags itself along with difficulty by its front feet; rectal temperature 33°.

Killed by section of the medulla.

Vesical mucous membrane shows hemorrhages in dots; no blood in the ureters or in the pelvis of the kidneys. Nothing unusual in the lungs, heart, or brain. No hemorrhage or congestion of the spinal cord; but on the level of the last two thoracic and the first two lumbar vertebrae there exists a softening of the spinal cord so advanced that at certain points (last thoracic), the spinal marrow runs like cream. The microscope shows the nervous elements intact, without a trace of bloody effusion.

Experiment DXXV. June 17. Cat.

From 12:20 to 1:30, taken to 10 atmospheres. At 1:39, decompressed suddenly in 3 minutes. When taken from the apparatus, runs in all directions as if panic-stricken. At 1:48, begins to be paralyzed in the hindquarters; at 1:50, lies on its side, unable to rise. Pupils contracted, the left more than the right; rectal temperature 39.5°; pulse 140, regular; respiratory rate 36, difficult, irregular. Motility and sensitivity completely gone in the hindquarters and the tail. 2 o'clock. No respirations; action of the heart still regular.

Immediate autopsy. Auricles still contract; on pricking the right auricle, frothy blood containing air issues; the left auricle, on the contrary, contains no air. On exposing the spinal marrow, we see in veins of the meninges a great quantity of small air bubbles; these bubbles also issue from the vessels of the spinal marrow when it is cross-sectioned. No sign of hemorrhage or congestion in the cord.

Experiment DXXVI. June 22. Cat of Experiment DLXVII (placed with the rabbit of DXX). 3:20, began the compression. At 4 o'clock, 5½ atmospheres; the motor stops. Began again at 4:20; at 4:45, 8 atmospheres. Current of air maintained under pressure.

At 4:50, decompression in 3 minutes. The cat leaps out of the apparatus and flees. At 5 o'clock, it is seized by an attack of convulsions, with violent struggling which lasts about 5 minutes. During these disordered and indescribable movements, the hindquarters progressively stiffen and become motionless, while the forequarters and the head are prey to the strangest contortions. Repeatedly the animal,

which is curled up, turns backwards and bites his hind legs and thighs with a kind of fury.

After 5 minutes, relatively calm; the left pupil dilated inordinately; almost complete paraplegia. Defecation by intestinal contraction, the anal sphincter not being paralyzed. Urination; no blood or sperm. 5:30. I show the animal to the Society of Biology; the paraplegia is complete as to movement and sensitivity. The pupils are in their normal state. 5:45. Apparent improvement; the left leg is sensitive, and the animal moves it a little, and when I support it, even leans on it a little; nothing in the right leg. 6:15. The right leg recovers a little in its turn; the tail begins to be sensitive.

June 23. The paraplegia has become complete again, and has even spread a little into the lower dorsal region. The following days, paralysis still more complete and extending a little higher. Dies June 26, the bladder distended; it could not be made to urinate; it ate.

Autopsy. All the spinal marrow is softened a little; it is diffluent below the cervical enlargement. At this precise point, it is a little yellowish, and contains a little altered blood and some granular bodies in the process of formation; the veins of the meninges contain a mixture of air and blood; air escapes from the vessels of the spinal cord. Sugar in the liver, a little in the urine, which also contains a little blood.

E. Experiments Made on Dogs.

Experiment DXXVII. May 17. Dog weighing 4 kilos. Pressure raised to 4 atmospheres. After about ¼ of an hour, opened the large cock suddenly; decompression in less than 2 minutes. The animal is in good shape.

Experiment DXXVIII. June 18. Small dog. Taken in one hour to 10 atmospheres; stays there about 1 hour; decompressed in 3 minutes. The animal cannot get out of the apparatus; there are no other movements than those of respiration; constant cries of pain.

Placed on the autopsy table, gas is observed in the jugular which has been exposed. Through the jugular a cannula is passed into the right heart, from which is extracted 33.9 cc. of gas containing 20.8% of CO_2 and 79.2% of nitrogen, with some traces of oxygen. The right heart and the veins are full of gas and frothy blood; the same thing is true of the veins of the pia-mater and the choroid plexuses. Stomach much distended by gases.

Experiment DXXIX. July 9. Dog weighing 12 kilos.

1:45: taken to 5 atmospheres; left 30 minutes under a current of air. Decompressed in 2 minutes. No immediate or delayed symptom.

Experiment DXXX. July 13. Dog which has lost much blood. Taken to 6 atmospheres and decompressed in 2 minutes. The animal drags its hind legs and walks on its nails; after an hour, walks better, but lies down again as soon as we stop stimulating him. Better the next day.

Experiment DXXXI. July 17. Dog of Experiment DXXIX and Experiment DLXXI (slow decompression).

From 1:36 to 2 o'clock, taken to 6 atmospheres; left 30 min.

Decompressed in 2 minutes; comes out in good condition, shakes himself, and walks very well. No symptom.

Experiment DXXXII. July 22. Dog.

From 5:30 to 6:10 taken to 6½ atmospheres. I then draw blood from which no free gases escape in the syringe. However this blood contains 7.7% of nitrogen. At 6:40, reached 8½ atmospheres; decompressed in 3 minutes. At 6:50, I draw blood from the carotid; this blood contains 2% of nitrogen.

The animal has remained fastened on the operating table; while sewing up the wound in the neck, I see bubbles of air in the jugular; it begins then to take deep breaths, which end in death at 7:15. No gas is found in the blood of the right or left heart; but there are numerous bubbles in all the little veins of the general and the portal systems. The stomach is enormously distended; 550 cc. of gas is drawn from it; the intestine contains much gaseous froth and is swollen with it.

Experiment DXXXIII. July 24. Dog of Experiment DXXXI.

From 3:30 to 3:55, taken to 6 atmospheres; left 2 hours under a current of air. Decompressed in 2 minutes, no symptom.

Experiment DXXXIV. July 25. Dog of preceding experiment.

From 2 o'clock to 2:45, taken to 7 atmospheres.

Decompressed immediately in 2 minutes: jumps alone from the top of the apparatus. Five minutes after, falls on its side, its hindquarters paralyzed; sensitivity much dulled. The front feet are in forced extension and quiver at each breath.

July 27. Complete paraplegia of movement; muscles relaxed; tail and feet insensible, but with reflex movements of the tail. The anal sphincter is relaxed, but the introduction of a thermometer provokes violent reflex movements; temperature 39.5°. Bladder paralyzed; when the belly is pressed, the urine issues in jerky spurts; it overflows regularly; no sugar.

August 1. The animal has remained lying on its right side; the paralysis has made ascending progress; the ribs are motionless, and the respiration is purely diaphragmatic; we then see clearly the lifting of the lower ribs by the diaphragm.

On pinching the right hind foot, it draws away, as does the tail: no movement in the left hind foot. The left sciatic, when exposed and pinched vigorously, causes some slight movements in the flexor muscles of the leg, but the animal feels nothing. The right sciatic gives marked movements, and the animal shows pain when it is pinched. The muscles tested by electricity require for contraction a current a little stronger on the left than on the right, which is no doubt due to the different action of the nerves. The toes of the hind feet, when taken in the hands, are warmer than the toes of the front feet; the latter are sensitive and are drawn away when pinched. The anal sphincter contracts convulsively when touched; the rectal temper-

ature is 38°. The urine issues when the right sciatic nerve is stimulated: no sugar. I kill the animal, which is very sick, by opening the thorax.

The left sciatic nerve is reddish, its vessels are bloodshot; in most of its fibers the myelin is a little turbid and is beginning to separate. The right sciatic nerve is intact.

The spinal cord is softened in the region of the lumbar enlargement. Transverse sections show the following changes. Below the enlargement, red dots in the gray matter; in the upper part of the enlargement, where section is possible, we find complete suffusion of the left posterior horn of the gray matter and suffusion in parts of the horn on the right side; the antero-lateral and posterior columns on the left are of a very marked yellowish-gray; all of it is very soft.

Below the dorsal region, uniformly red appearance of all the gray matter, which is less soft, with coloration spreading into the posterior white matter, especially on the left; yellowish gray softening of the left antero-lateral column and the posterior column.

The alteration lessens as it goes upward and ceases above the brachial enlargement; the cord there is firm, but a little suffused.

Experiment DXXXV. August 3. Dog.

At 8 atmospheres, the little apparatus, which supports the cannula for drawing blood (Fig. 34, E), is violently thrown forward: the pressure falls in 3 or 4 minutes.

The dog comes out, runs a few steps, then falls and dies rapidly. Gas in abundance in the right heart, but not in the left heart.

Experiment DXXXVI. August 5. Pregnant bitch taken to 9¼ atmospheres, bled of 375 cc. of blood (See Exp. CLXXXIV)[1]; decompressed rapidly: takes a few breaths and dies.

Both sides of the heart are full of gases almost completely free: the stomach contains little gas.

The hearts of the foetuses and their veins contain both gas and a very dark blood. In the allantoid liquid abundant bubbles are floating; the placenta is all torn by the gases; no gas in the amnion.

Experiment DXXXVII. October 16. Dog which has already served for Experiments DLXXVII and DLXXVIII (10 atmospheres, slow decompression). From 1:10 to 1:45, taken to 7 atmospheres, decompressed at 1:55 in 2½ minutes.

Taken from the apparatus, is lively and seems to feel no painful symptom. 3½ minutes after the decompression, raises its right front foot and seems to be in pain. After 5 minutes, struggles, wavers in its hindquarters, has an almost sudden erection. After 7 minutes, enormous convulsive stiffening of the hindquarters, which one can hardly bend. The tail moves and the front legs are not affected.

The animal is recompressed to 7 atmospheres and decompressed very slowly. (See Exp. DLXXXVIII.) Dies the next day.

Experiment DXXXVIII. October 18. Dog.

From 2:25 to 3:10 compressed to 7 atmospheres, and left 7 minutes. Decompressed as rapidly as possible, in 2 minutes, from 3:17 to 3:19. Withdrawn from the apparatus, comes, goes, fawns; but at 3:21

is seized by paralysis of the hindquarters; he soon remains lying down, and his sufferings are shown by howls.

Taken to 7 atmospheres again, and then to an extremely slow decompression. (See Exp. DLXXXVII.) Dies in the evening.

Experiment DXXXIX. October 20. Dog.

Subjected to 3½ atmospheres. Arterial blood drawn under mercury in a test tube. Very small bubbles of gas are plainly escaping, and collecting at the upper part of the tube.

Decompressed in 1 minute, shows no symptom; the heart sounds are normal.

Experiment DXL. October 23. Same animal taken to 4½ atmospheres, and left 10 minutes. Decompressed in 1¼ minutes, experiences no symptoms immediate or delayed.

Experiment DXLI. October 25. Same animal taken to 5 atmospheres; left 10 minutes and decompressed in 1¾ minutes. Still no symptom.

Experiment DXLII. October 31. Dog.

Taken to 7¼ atmospheres. Decompressed in 1¼ minutes. Taken out at 2:07, without immediate symptoms.

At 2:15, is found weak, staggering, has vomited several times. At 2:35, enormous gurglings heard in the heart, and the animal dies suddenly.

Gas in the heart and the whole venous system, even the portal vein. Nothing in the left heart.

Experiment DXLIII. October 31. Dog.

Placed beside the former; has no immediate symptom. But at 2:15 is found lying on its side motionless; respiration is difficult, whistling, as if the animal were going to die soon. There are gurglings in the heart.

He is made to inhale oxygen (See conclusion, Exp. DLXXXIX). He dies during the night.

Experiment DXLIV. November 12. Dog.

Taken to 7¼ atmospheres. Decompressed in 2 minutes. Dies in about 25 minutes. Free gas in all the little veins; right heart full of foam; bubbles less numerous in the left heart.

Experiment DXLV. November 12. Dog.

Placed beside the former. Seized by symptoms of paralysis and dies after about 1½ hours, after he has been given oxygen. (See Exp. DXC.)

Experiment DXLVI. November 15. Dog.

Taken to 6½ atmospheres; decompressed in 4½ minutes. No symptom; no gas in the blood of the jugular vein, which I examined with the microscope to make more certain.

Experiment DXLVII. November 25. Bitch.

From 2:25 to 3 o'clock taken to 7½ atmospheres.

At 3:14, decompressed in 2½ minutes.

At 3:23, is paralyzed in the hindquarters, then falls; in a few minutes, respiration stops, and the heart beats only 20 times per minute; loud gurgles heard in the heart; eye lacks sensitivity, pupils dilated.

Oxygen administered, but the animal dies at 3:35. (See Exp. DXCI.)

Experiment DXLVIII. November 27. Very small poodle.

Raised to 7 atmospheres from 3 o'clock to 3:53.

Decompressed in 2¼ minutes.

Taken from the apparatus, seems gay for a few minutes, then, at 4:10, begins to limp, is paralyzed in the hindquarters, and suddenly falls on its side. Very loud gurgles in the heart.

Oxygen administered, but the animal dies at 4:27. (See Exp. DXCII.)

Experiment DXLIX. December 6. Short-haired dog, very lively.

Put under pressure from 2:30 to 4:20 and taken to 7½ atmospheres.

At 4:20, decompression in 2 minutes.

Leaves the apparatus. At the end of 10 to 15 minutes, is paralyzed in the hindquarters, and seems quite ill with perhaps gurgling in the heart (?).

Then recovers a little, but yet cannot stand on its hind legs, which have retained sensitivity.

December 7. Is still paraplegic and can hardly stand on its front legs. Reflex movements, reflex sensitivity in the hind legs, which are warmer than the front legs.

December 11. Scab on the left shoulder, on which it is lying; odor of urine; hyperesthesia in the front feet; dying.

Experiment DL. December 6. Spaniel, placed beside the preceding animal.

Remained in the apparatus from which it was removed paraplegic, with very loud gurgles in the heart. It was given inhalations of oxygen. (See the continuation of its history, Experiment DXCIII.)

Experiment DLI. December 22. Dog.

Taken to 8½ atmospheres. Decompressed in 2½ minutes.

Taken from the apparatus, is already limp, and dies in 5 or 6 minutes. Air in great quantity in the right heart and the veins. Some bubbles in the left heart. Gas in abundance in all the vessels of the lower region of the spinal cord.

Experiment DLII. January 16. Bitch weighing 6.5 kilos, in bad state generally.

Taken to 7½ atmospheres, then decompressed suddenly. No symptom immediate or delayed.

Experiment DLIII. January 23. Same animal.

Taken again to 7½ atmospheres and decompressed suddenly. About 10 minutes afterwards, bites its hindquarters, as if it felt keen pains there; it then seems to have some trouble in locomotion, but this disappears quickly.

Experiment DLIV. January 25. Same animal.

Taken to 8 atmospheres, and decompressed suddenly. No apparent effect.

Experiment DLV. January 29. Same animal.

Taken to 8½ atmospheres, and decompressed suddenly.

Experiences a little irregularity and difficulty in the hindquarters, but seems very gay, with no uneasiness; no gurgles in the heart; no gas observed in the jugular, which has been exposed.

Experiment DLVI. February 11. Same animal.

Compressed to 8 atmospheres and left under pressure 5 minutes, then decompressed in exactly 3 minutes.

At the fifth minute, after the beginning of the decompression, blood is drawn from the carotid; no gas found in it.

At the tenth minute, blood drawn from the right heart with a cannula: no gas there either.

No symptom.

Experiment DLVII. February 12. Sickly dog, very thin, weighing 8 kilos.

From 4:30 to 5:32, taken to 8 atmospheres; decompressed in 3 minutes.

Placed on the floor, does not seem at all uneasy, and walks.

At 5:42, the hindquarters become stiff and motionless.

At 5:55, the forequarters are similarly affected; great respiratory distress.

Dies at 6:05. Air in the veins.

Experiment DLVIII. February 27. Poodle weighing 7 kilos.

Placed in the apparatus at 8 o'clock in the morning, at 9:30 is at 10 atmospheres; the pump is stopped.

At 10 o'clock, the pressure is only 9¾.

At 10:30, I look at the animal; it is well, and puts its nose against the porthole; the pressure is 9½ atmospheres.

I enter the laboratory again, and immediately a violent explosion is heard. The porthole glass has burst and its fragments had enough force to cut a lead water pipe one meter away; the apparatus was lifted, torn from its supports by the recoil, and overthrown.

I take the animal out with great difficulty, for it has become cylindrical, and is hard to pull through the door. General subcutaneous intra- and submuscular emphysema. I open the belly; the gas which distends it escapes whistling.

The right heart is full of gas, as are all the veins, the pulmonary artery, and the pulmonary veins. But there is none in the left auricle or the aorta. There is gas in the anterior chamber of the eye, and in the cerebro-spinal liquid. The nerve fibres of the spinal cord are dissociated by bubbles of gas, which are not in the vessels.

There is no hemorrhage in the brain or the cord; the lungs are a little congested: no blood in the trachea.

I extract 50 cc. of gas from the right heart (there is much more of it) taking all precautions to prevent entrance of air. This gas contains per 100 parts: O_2 1.9; CO_2 15.1; N 83.0.

Experiment DLIX. May 6. Dog weighing 11 kilos.

From 1 o'clock to 1:58, compressed to 7½ atmospheres.

I maintain a current of air under pressure until 7 o'clock, when I make the decompression in 3 minutes.

On leaving the apparatus, the animal staggers, then stops, falls, and dies.

There are abundant bubbles of air in the right heart and the veins, tiny bubbles in the left heart.

No gas in the subcutaneous cellular tissue, except in the hollows of the armpits; gas is also found in small bubbles in the tissue of the epiploon.

The intestines do not appear more swollen than under ordinary conditions.

Experiment DLX. June 3. Bitch of Experiments DLII to DLVI. Well fed, has become fat and very well.

From 3:05 to 4:05 was taken to 8 atmospheres and decompressed immediately in 1¾ minutes.

Taken from the apparatus, it runs everywhere, apparently gay, and wagging its tail.

But after 3 or 4 minutes, utters pitiful howls and tries to bite its hindquarters, which begin to be paralyzed.

Auscultation of the heart shows considerable gurgling on the right, but not on the left.

Two or three minutes later, the howls cease, the paralysis, both of sensibility and movement, is complete.

It increases, affects the whole body, with rigors in the legs and neck. The respiration, which for a long time has been merely diaphragmatic, becomes very difficult; the heart slows down and the animal dies about 4:30.

I find gas in the general venous system and the portal vein, but not in the arteries.

There is emphysema in the subcutaneous tissue of the armpits; there are innumerable little bubbles in the fatty tissue under the muscles of the thorax, and in the sub-aponeurotic layer all along the back, in the epiploon, the mediastinum, the furrow of the heart, and the fatty tissue of the medullary canal.

Index of air in the vessels of the medullary and cerebral pia-mater: nothing in the velum interpositum, or the cerebro-spinal liquid.

No blood effusion in the brain; rather large dotting on the spinal cord. Lungs healthy, without congestion or emphysema; congestion of the spleen; little suffusions of the great epiploon.

Experiment DLXI. July 21. Dog weighing 6.5 kilos.

From 2:30 to 4 o'clock, taken to 8 atmospheres.

At 4:10, decompressed in 1¼ minutes.

Dies at 4:22, with air in quantity in the whole venous system; small bubbles in the left heart.

Lungs blood-shot, edematous.

Experiment DLXII. May 24. Large spaniel.

(Experiment made before the Committee of the Academy of Sciences.)

Compression raised to 8½ atmospheres, and decompression made in 2 minutes.

The dog appears gay and runs about wagging his tail. After a few minutes, he sits down and becomes sad. Some minutes later, he falters on his front legs and falls down.

Gurgles can be heard in the right heart.

The animal seems to be in great pain and bites violently at whatever is held out to him. He soon dies.

Gas in fine bubbles in the whole venous system; none in the arteries.

Experiment DLXIII. June 4. Young dog in good health, weighing 4.500 kilos.

The jugular vein is exposed without being opened; the animal, fastened on the operating board, is carried to the compression apparatus, and rapidly taken to 6 atmospheres, and this pressure is maintained under a current of air for 3½ hours. It howls a great deal.

Decompression in 20 seconds. The animal is taken from the cylinder and unfastened. Complete paralysis of movement and of sensibility in the four legs; rapid pulse, accelerated respiration; no howls.

Put back immediately on the operating table; 50 cc. of blood are drawn from the peripheral end of the jugular; no gas to be seen; blood is slowly ejected under water; no gas bubbles. A cannula is inserted into the right auricle; 50 cc. of blood is drawn and treated in the same way; no bubbles.

The dog is attacked by diarrhea and involuntary urination.

It dies during the night.

The autopsy shows the presence of large bubbles of gas in the venous system (vena cava, azygos vein, mesenteric veins). Much is found in certain lobes of the liver and in the kidneys, a little in the spinal cord, no trace of it in the brain, the meninges, or the muscles.

Experiment DLXIV. June 12. Young white dog of small size, in very good health. Placed in the large cylinder; brought rapidly to 5½ atmospheres of pressure. Maintained under this pressure with a current of air for 4 hours.

The animal seems very quiet during all this time.

Decompressed in 20 seconds.

When taken from the apparatus, it runs away, and we have great difficulty in catching it. When the right jugular and femoral veins are exposed, we see passing a long series of gas bubbles which keep growing larger.

After a few minutes, by means of a syringe, we draw from the peripheral end of the jugular a certain quantity of blood which is gently ejected under water: immediately numerous bubbles are seen escaping to the surface.

Dog, kept under observation for several days, shows no delayed symptom.

I summarize in the following table the principal results furnished by the experiments just read. I have listed them here by increasing order of pressures.

I have included in this table the results of experiments in which I attempted to save the animals, either by recompressing them or by administering oxygen. (See Subchapter IV.)

Table XVIII

Experiment number	Duration of compression	Pressure in atmospheres	Duration of Decompression	Condition of animal
		Sparrows		
DXV	slow compr.	7	instantaneous	Dead in a quarter of an hour. Two animals.
DV	5 min.	8	a few sec.	No symptoms.
DIX	2 min.	8	id.	id.
DVI	2 hours	8	id.	Died in 10 min. Gas in the blood.
DVII	1 h. 35 min.	9½	id.	No symptoms.
DX	a few min.	10	id.	id.
DXI	id.	12	id.	Died almost immed. Gas in abundance.
DXII	id.	14	id.	Died in few minutes. Gas in abundance.
DXIII	id.	14	id.	No immediate symptoms. Dead next day.
DXIV	id.	15	id.	Died quickly. Gas in abundance.
DVIII	5 min.	16	id	Died in a few minutes. Gas: convulsions from oxygen had begun.
		Rats		
DXVII	1¼ h.	5½	a few sec.	No symptoms.
DXVIII	1¾ h.	6½	——	id.
DXVI	¾ h.	6½	a few sec.	No symptoms.
DXIX	----	8½	2 min.	Two animals. Dead in a few minutes. Gas in the blood.
		Rabbits		
DXXIII	1¾ h.	6½	4½ min.	No symptoms.
DXXI	a few min.	7	2 to 3 min.	Two animals.
DXX	5 min.	8	id.	id.
DXXII	----	8⅛	id.	Two animals.

Table XVIII—Continued

Experiment number	Duration of compression	Pressure in atmospheres	Duration of Decompression	Condition of animal
		Cats		
DXXVI	5 min.	8	2 to 3 min.	Paraplegia, dies in 4 days; medullary softening. Exp. made at the same time as Exp. DXX.
DXXV	9 min.	10	id.	Dies in 15 min. Gas in the blood.
DXXIV	----	10	id.	Killed next day. Medullary softening.
		Dogs		
DXXXIX	----	3½	1 to 2 min.	No symptom, yet tiny bubbles of gas escape from the blood.
DXXVII	15 min.	4	2 to 3 min.	No symptoms.
DXL	----	4½	id.	id. Same animal as in Exp. DXXXIX.
DXXIX	30 min.	5	id.	id.
DXLI	----	5	id.	id. Same animal as in Exp. DXL.
DLXIV	4 hours	5½	20 sec.	Gas in the veins; no symptoms.
DXXXI	30 min.	6	id.	id. Same dog as in Exp. DXXIX.
DXXXIII	2 hours	6	id.	id. Same dog as in Exp. DXXXI.
DXXX	a few min.	6	id.	Drags hind-quarters a little. Recovers.
DLXIII	3 h. 30 min.	6	20 sec.	Immediate paralysis; no gas. Dies; gas everywhere.
DXLVI	a few min.	6½	4½ min.	No symptoms. No gas in jugular blood.
DXXXIV	id.	7	2 min.	Paraplegia, medullary softening. Dies in a week. Same dog as in Exp. DXXXIII.
DXXXVIII	7 min.	7	2 min.	Paraplegia; recompressed and decompressed slowly. Dies in the evening.
DXXXVII	10 min.	7	2½ min.	Paraplegia; recompressed and decompressed slowly; dies next day. No gas in blood. Small bloody spots in spinal marrow.
DXLVII	15 min.	7½	2 min.	Paralyzed, much gas in heart; dying. Oxygen inhaled; respiration restored; accident; death.
DXLVIII	a few min.	7	2¼ min.	Paralyzed; oxygen inhaled; dies.

Table XVIII—Continued

Experiment number	Duration of compression	Pressure in atmospheres	Duration of Decompression	Condition of animal
DXLIV	id.	7¼	1¼ min.	Paralyzed, dies after 25 min. Gas in heart.
DXLIII	id.	7¼	1¼ min.	Paralyzed, inhales oxygen, respiration resumed, gurgles disappear. Remains paralyzed, dies; no air in blood vessels.
DXLIV	id.	7¼	2 min.	Dies in 25 min. Gas in right and left heart.
DXLV	id.	7¼	2 min.	Paralyzed, dying; breathes oxygen; better, gurgles disappear; moves, uneasy, dies after 1½ hours; no gas in blood vessels.
DXLIX	id.	7½	2 min.	Slightly sick, recovers, slightly paraplegic.
DL	id.	2½	2 min.	Paralyzed; gurgles. Oxygen. Gas disappears, animal survives, paraplegic. Dying on third day.
DLII	id.	7½	2 min.	No symptoms.
	id.	7¾	3 min.	Oxygen inhalations. The beginning paralysis is checked, but dog remains paralyzed several days.
DXXXV	id.	8	3 or 4	Dies quickly. Gas in right heart.
DLVII	id.	8	3 min.	Dies in quarter of an hour. Gas in veins.
	id.	8¼	3 min.	Oxygen inhalations. Paraplegia, no gas in heart; better; dies during night.
DLI	id.	8½	2½ min.	Dies quickly. Air everywhere.
DLIII	id.	7½	2 min.	Animal of Exp. DLII. Slight locomotor and sensory disturbances.
DLIV	id.	8	2 min.	Same animal. Nothing.
DLVI	id.	8	2 min.	Same animal. Nothing. No gas in blood.
DLV	id.	8½	2 min.	Same animal. Slight locomotor disturbances. No gas in the blood.
DXXXII	id.	8½	3 min.	Rapid death (25 min.). No gas in heart; gas in all small veins, portal vein, and vessels of the medulla; 550 cc. of gas in the stomach.

Table XVIII—Concluded

Experiment number	Duration of compression	Pressure in atmospheres	Duration of Decompression	Condition of animal
DXXXVI	id.	9¼	3 min.	Blood drawn at 3 atm. released free gases. Died after a few breaths. Gas everywhere. She is pregnant; gas in blood of foetuses and allantois; placenta torn.
DXXVIII	id.	10	3 min.	34 cc. of gas drawn from right heart (CO_2 20.8; N 79.2; O_2 traces). Gas in vessels of pia mater.
DLVIII	1 hour	9½	Explosion	Instantaneous death. Huge subcutaneous and submuscular emphysema, gas in belly, in epiploon, the anterior chamber of the eye, the cerebro-spinal liquid, the spinal cord. No hemorrhage in spinal cord, brain or lungs. No gas in left heart. Right heart full of gas (CO_2 15.2; N. 82.8; O_2 2.0).
DLIX	5 hours	7½	3 min.	Rapid death; subcutaneous emphysema. Gas all through blood.
DLX	a few min.	8	1 m. 45 sec.	Animal of Exp. DLII to DLVI. Dies. Gas in venous system; subcutaneous emphysema.
DLXII	id.	8½	2 min.	Dies. Gas in veins.
DLXI	10 min.	8	1¼ min.	Dies in 12 min. Gas in veins and left heart.

2. Slow Decompression or Decompression in Stages.

The preceding data furnish ample material for a fairly complete account of the curious phenomena due to sudden decompression and for an explanation of them. However, there is such variety in the details that it seems best to report in addition a certain number of experiments of the same type, in which, however, the decompression was made more slowly, for the purpose of finding out the precautions that must be taken if the decompression is to be harmless.

Here are these experiments:

Experiment DLXV. June 20. Guinea pig. From 2:45 to 3:50 brought to 10 atmospheres; I establish a current of air under pressure.

At 4:04, opened the cock wide; in 1 minute, the pressure falls to 5 atmospheres; I then keep the cock open a little; the pressure is down to normal at 4:30.

Opened the apparatus: the guinea pig seems in good condition; but at 4:40, he struggles, rolls up, is paralyzed in ascending progress, the respiration is disturbed, and stops at 4:45.

Gas in abundance in the right heart, in the veins of the legs and the arteries. No gas in the left heart, the pulmonary and coronary veins, and the portal system.

No gaseous distention of the stomach and the intestines.

Experiment DLXVI. June 20. Cat, placed beside the guinea pig of the preceding experiment.

Taken to 10 atmospheres. Dropped in 1 minute to 5 atmospheres, then in 25 minutes to normal pressure.

No immediate or delayed symptom.

Experiment DLXVII. June 29. Cat and rabbit brought in 1½ hours to 10 atmospheres. Pressure maintained under a current of air for 5 hours.

Decompression in 2 hours.

They are taken out all wet, trembling (the cat was trembling in the apparatus in the compressed air), they did not cry out; no paralysis; they recover rapidly and survive.

The temperature of the cat has fallen from 39.5° to 34.3°; that of the rabbit from 39.6° to 36.7°.

Experiment DLXVIII. July 2. Rabbit of Experiment DXX. From 2:50 to 3:55, raised to 10 atmospheres; current of air for 30 minutes.

The decompression is begun at 4:27; it is made with calculated slowness, watch in hand, at the rate of about 1 atmosphere per 2 minutes; it is finished at 4:47.

The rabbit seems well. However, it is seized by paraplegia about 6 o'clock, still preserving its sensibility; still living at 7:30; found dead the next day.

Experiment DLXIX. July 2. White cat placed beside the rabbit of the preceding experiment.

Taken to 10 atmospheres, decompressed regularly in 20 minutes.

The white cat cries out, breathes with difficulty; at the end of a few seconds, seems furious, bites itself, bites the gray cat of the following experiment, which is stretched out near it. Has convulsive quiverings; its pupils are very much dilated. Dies in 5 minutes. With the greatest precaution I draw gas from the right heart; the 23.8 cc. of gas which I obtain thus contain 15.9% of CO_2, the rest is nitrogen, without a trace of oxygen.

Gas in all the circulatory system: veins, arteries, portal system, inner vessels of the spinal cord. The latter is very hard and shows no sign of tearing.

Experiment DLXX. July 2. Gray cat, placed beside the animals of the two preceding experiments.

Is dying when taken out, and dies immediately afterwards.

I draw from its right heart 33.1 cc. of gas, which contains 17% of CO_2.

Same results at autopsy as in the preceding experiment.

Experiment DLXXI. July 10. Dog of Experiment DXXIX.

From 2:40 to 3:40, taken to 10 atmospheres. As it approaches 10 atmospheres, has a sort of convulsion.

Under pressure for 30 minutes.

Decompressed from 10 to 6 atmospheres in 1 minute; then from 6 to 1 in 1 hour. Same convulsions during the decompression.

As it leaves the apparatus, it cannot stand up on its hind legs; howls and whimpers; lies down on its side; trembling and strong extension of its front feet at every inspiration. Hind legs flexed, motionless, but sensitive.

About 5:30 gets up, walks a little, slowly, then lies down again, still weak in the hindquarters.

July 11. Well.

Experiment DLXXII. July 23. Dog of Experiment CLXXXII.

At 5:08, dog taken to 10 atmospheres; at 5:15, dropped in 2 minutes to 6 atmospheres; at 5:45, dropped in 2 minutes to 3 atmospheres; at 6:33, decompressed in less than 30 minutes.

No immediate or delayed symptom.

Experiment DLXXIII. July 27. Dog of Experiment CLXXXIII.

Taken to 10 atmospheres, 143 cc. of blood drawn.

Decompressed at the rate of 1 atmosphere per 3 minutes, very regularly.

The operation is over at 5:45.

Removed at 6 o'clock, is paraplegic: right leg almost insensible, left one slightly sensitive, tail sensitive.

At 7 o'clock, difficult breathing. Ascending paralysis which has invaded the whole body; the ribs no longer move; breathing purely diaphragmatic.

Found dead the next day.

Experiment DLXXIV. August 7. Bitch taken to 10 atmospheres, 128 cc. of blood drawn. (See Exp. CLXXXV.)

I make the decompression by means of the graduated cock; in 20 minutes, the pressure drops 2½ atmospheres; in the following 20 minutes, it drops 1¼ atmospheres, and 1¾ atmospheres in the following 16 minutes; it is then 4½ atmospheres, and I open the large cock, which restores normal pressure in 3 minutes.

It is all finished at 7:31.

Removed at 7:40, the animal is completely paralyzed; gurgling heard in the heart: 80 extremely irregular heartbeats; 80 to 100 respirations, still operated somewhat by the ribs; no apparent uneasiness; great quantity of froth in the mouth.

Dies at 8 o'clock.

Left heart: dark blood with a little gas. Right heart: dark blood frothy with fine bubbles of gas.

Gas in all the veins and arteries, except the veins of the portal system, while the mesenteric arteries are full of it.

Abundant foam in the stomach and intestine, but not enormous or dangerous from its volume. Foam in the bronchi: lungs healthy, without congestions and effusions.

Experiment DLXXV. August 8. Dog taken to 10 atmospheres, and bled of 133 cc. (See Exp. CLXXXVI.)

Decompressed in 50 minutes, very regularly, that is, about 5 minutes per atmosphere.

Normal pressure established at 7:30.

At 7:35, very loud gurgling heard in the heart. The animal, when placed on the floor, is paralyzed in the hindquarters and the ribs. Rectal temperature 39°.

8:30, very loud gurgling on the right, much less on the left; progressive paralysis; the animal is conscious and raises its head when called; rectal temperature 36°.

9:30, state still more serious; temperature 35°; the eyes are almost the only movable parts. Still loud gurgling on the right, less on the left.

Found dead the next day.

Experiment DLXXVI. August 9. Dog.

Taken from 8 o'clock to 9:12 to 10 atmospheres; seems to undergo a sort of convulsive struggling in the apparatus.

Decompressed very regularly in 1 hour and 30 minutes, that is, 10 minutes per atmosphere.

Taken out at 10:42, gay and well.

At 10:47, the left front leg stretches out, then is paralyzed in movement but remains sensitive.

At 10:50, the animal falls, the right hind leg is stretched out, paralyzed in movement.

10:55, this leg is better, but the left hind leg is affected in its turn.

11 o'clock, the whole left side is paralyzed, but sensitive.

Experiment DLXXVII. October 25. Vigorous dog placed free in the large apparatus.

From 2:30 to 4 o'clock, the pressure is taken to 10 atmospheres. About 3:50 the dog, which has howled all the time it has been in the apparatus, is seized by an attack of tonic and clonic convulsions which lasts some 20 seconds.

After this, it remains weak and staggering for some minutes.

At 4:10, the animal seems well; decompression is made by passing abruptly from 10 atmospheres to 8, from 8 to 6, from 6 to 4, from 4 to 2, from 2 to 1. At each stage, a pause of 15 minutes is made. The whole decompression lasts 1 hour and 10 minutes.

No symptom has appeared during the decompression. The cylinder is opened, and the animal comes out freely. But after 2 or 3 minutes, it utters cries of pain.

At 5:45, it lies down; the hindquarters are stiff; when it is forced to stand up, it lifts the left front foot, which seems to give it pain.

At 6:15, is howling less, but is still in the same state.

Well the next day.

Experiment DLXXVIII. October 28. Dog of the preceding experiment, quite recovered.

Taken to 10 atmospheres; after 5 minutes, has an attack of convulsions. At the end of 15 minutes, decompression is made at the rate of 8 minutes per atmosphere, very regularly, the whole requiring 1 hour 12 minutes.

Shows no symptom either immediate or delayed.

Experiment DLXXIX. November 14. Dog.

Taken to 9 atmospheres. Decompressed in about 1 hour.

When taken from the apparatus, its rectal temperature is 20°. It has loud gurgles in the heart and soon dies.

Experiment DLXXX. June 27. Dog weighing 19.3 kilos.

From 1 o'clock to 2 o'clock is raised to 7½ atmospheres, with a current of air. A leak develops; at 3 o'clock, the pressure is 6 atmospheres; at 6:45 it is only 4½ atmospheres, in spite of the constant pumping.

Decompressed from 6:45 to 7:45.

When taken out, the big dog is very wet, cold, dying; it dies after a few breaths. Pulmonary ecchymoses are found, and gas everywhere in the blood.

Experiment DLXXXI. June 27. Two puppies, very young, weighing about 1.5 kilos.

Placed beside the animal of the preceding experiment.

The puppies are also very wet; but they show no symptom, either immediate or delayed.

I summarize in Table XIX the data relating to the progressive and slow decompression.

3. Summary and Conclusions from the Preceding Experiments.

Let us now consider these experimental results in their entirety. The first striking fact when we examine Table XVIII is that sudden decompression is much less dangerous to birds than to mammals. A sparrow, in fact, (Exp. DX) survived the decompression from 10 atmospheres, another (Exp. DXIII) did not die for a long time after a decompression from 14 atmospheres.

On the contrary, in mammals, symptoms began to appear at 6 atmospheres (Exp. DXXX); death struck almost all the animals decompressed from 8 atmospheres, and all of those decompressed from 9. Dogs and cats seemed even more susceptible than rabbits; Experiments DXX and DXXVI made simultaneously on a cat which died and a rabbit which survived, are characteristic, except for individual differences.

In the same species, in fact, we notice differences which are very important. In dogs, for example, we have always had severe

Table XIX

Numbers	Species of animal	Pressure	Duration of decompression	Condition of animal
DLXVII	Rabbit	10	5 hours of compression;	No symptoms.
	Cat		decompressed in 2 hrs.	No symptoms.
DLXVIII	Rabbit	10	2 m. per atm. 20 min.	Paralyzed after 1 hour, lived more than 3 hrs.
DLXIX	Cat	10	2 m. per atm.; 20 min.	Dies in 5 min. 23 cc. of gas in heart (CO, 17, N. 84.1).
DLXX	Cat	10	2 m. per atm. 20 min.	Taken out dying. 33 cc. of gas in heart (CO, 17, N. 83).
DLXV	Guinea pig	10	From 10 to 5 atm. in 1 min.; from 5 to 1 in 30 min.	Dies in 15 min.; gas in venous system only.
DLXVI	Cat			No symptom.
DLXXXI	Puppies		1 hour from 7½ to 6;	No symptom.
DLXXX	Adult dog	7½	3 h. 45 min. from 6 to 4½; 1 h. from 4½ to 1.	Withdrawn dying. Gas everywhere.
DLXXIX	Dog	9	In about an hour	Dies quickly.
DLXXIII	id.	10	3 min. per atm. 27 min.	Paraplegia. Died during night.
DLXXV	id.	10	5 min. per atm. 50 min.	Gurgling; progressive paralysis. Dies during night.
DLXXVIII	id.	10	8 min. per atm. 1 h. 12 min.	No symptom.
DLXXVI	id.	10	10 min. per atm. 1 h. 30 m.	Slight symptoms; survives.
DLXX	id.	10	From 10 to 6 in 1 min.; from 6 to 1 in 1 hour.	Slight locomotor disturbances; recovers. Animal of Exp. DXXIX.
DLXXIV	id.	10	From 10 to 7½, 8 m. per atm.; from 7½ to 6¼, 15 m. per atm.; from 6¼ to 4½, 9 m. per atm.; from 4½ to 1, 3 m. per atm. In all, 1 hour.	Completely paralyzed; gurgling; dies in 20 min. Gas in all the blood.
DLXXVII	id.	10	Abruptly from 10 to 8; from 8 to 6; from 6 to 4; from 4 to 2; from 2 to 1. At each stage, 15 min. pause. In all, 1 hour, 10 min.	Comes out of the apparatus without help; soon howls. Locomotor disturbances. Recovers and survives.
DLXXII	id.	10	From 10 to 6 in 2 min.; left 30 min. at 6. From 6 to 3 in 2 min.; left 45 min. at 3. From 3 to 1, about 15 min. In all about 1 hour, 30 min.	No symptom.

symptoms, often death, at 7 atmospheres, except the animals of Experiments DXLIX and DLII which resisted the decompression of 7½ atmospheres, and that of DLV which survived even 8½.

This last animal, from this point of view, is particularly interesting. In a series of sudden decompressions, beginning with 7½ atmospheres (Exp. DLII and DLIII), then with 8 atmospheres (Exp. DLIV and DLVI), and even 8½ atmospheres (Exp. DLV), it showed no sign of sickness. Then four months later, decompressed from 8 atmospheres, it died in less than a half-hour (Exp. DLX). During the first series of experiments, it was thin and in very bad shape; at the time of the last, on the contrary, good care had made it fat and healthy.

Must we attribute the difference in results to this difference in condition? The cause, purely physico-chemical, which we shall be compelled to attribute to the symptoms of decompression, does not lend itself to this interpretation. Furthermore, Experiment DLVII shows us a dog in just as bad a condition, at least, which at the first trial, died from a decompression beginning with 8 atmospheres.

No less inexplicable is the resistance of the puppies of Experiment DLXXXI when the adult dog placed beside them during more than 5 hours (Exp. DLXXX) died immediately after a slow decompression, beginning with 7½ atmospheres.

But setting aside these irregularities which may suggest important considerations in practice, let us now examine the symptoms in themselves.

In sudden decompression beginning with 8 atmospheres and above, we have seen almost always a practically instantaneous death. It appeared also, but more rarely, in decompressions beginning with 7 to 8 atmospheres. Generally then the symptoms consisted of a paralysis of the hind legs, a paralysis sometimes slight and transitory, sometimes persisting for several days, sometimes, finally, rapidly ascending and involving death by asphyxia after several hours.

The cases in which the paralysis receded were, as one might expect, the limited cases (Exp. DXXX, DLXXI, DLXXVI); the limbs alone had been affected; voluntary movement alone had been lessened. These symptoms disappeared of themselves in less than an hour; all that I saw last longer continued till death.

When death occurred, we usually found to explain it and to explain the more or less complex phenomena which had preceded it, a more or less extensive softening of the spinal cord, much advanced in the lumbar regions, and making progress in the rest of

the organs, in which inflammatory lesions like those described in Experiments DXXVI and DXXXIV preceded it.

There now remain to be explained at the same time the initial cause of these cases of paralysis of greater or less length, and the reason for the almost immediate death which so often occurred.

Let us say next that the hypothesis of M. Bouchard is not at all verified. We have indeed sometimes found the stomach and intestines slightly distended by gases; but, besides the fact that this distention has never been very great, we have never seen in the lungs or nervous centers the congestions and hemorrhages to which sudden death is due, according to this author. Furthermore, in all cases, we have noted the persistence of the heart beats, and therefore we must set aside also the idea of syncope.

We can go still further. The evident proof that the symptoms which attack decompressed animals are not due to abrupt oscillations of the blood which has been driven back by sudden expansion of the intestinal gases is easily drawn from the experiments reported in Chapter IV. We see indeed that dogs could be brought in a few minutes from 7 or 8 atmospheres to normal pressure without showing symptoms similar to those which have just been described, with which it is impossible to confuse the phenomenon of oxygen poisoning, of which they presented the strange and terrible picture.

But the true cause of all these symptoms was shown very clearly, and the hypothesis of MM. Rameau and Bucquoy (see page 501) received the strongest confirmation from our experiments. The gases of the blood, as the professor of Strasburg had foreseen, are liberated under the influence of sudden decompression, and then cause symptoms comparable to those of an injection of air into the veins. But the phenomenon is more varied and complex than the learned physicist could have thought it.

In the first place, it is not the three gases of the blood, as he thought, that thus regain their gaseous form. We might have foreseen this result, because our previous researches (Chapter II, Subchapter III) had showed us that the proportion of the oxygen is hardly increased by pressure, and that of the carbonic acid is not increased at all. We were therefore in a position to state, and we might have thought that we had the right to do so, that the gas which would threaten life on being liberated would be exclusively the one the proportion of which was considerably increased in the blood, that is, nitrogen.

This conclusion could also be drawn from the experiments of

Chapter IV to which I alluded a moment ago; here no symptom appeared, no gas bubble was freed in the vessels, because the air which the animals were breathing had a very low nitrogen content.

But there is better proof; I could, as Experiments DXXVIII, DLVIII, DLXIX, and DLXX show, extract the gases collected in quantity in the heart and analyze them. I did indeed find them composed chiefly of nitrogen; but I must confess that I was much surprised to find, besides the nitrogen, a quantity of carbonic acid which varied from 15% to 20% and even, in one case (Exp. DLVIII), a little oxygen.

The explanation of these facts should probably be drawn from the circumstances that the liberation of the nitrogen takes place in little bubbles, which the circulatory movements stir up before they can collect in the heart in vast collections of gas, so that the blood is, as it were, traversed by a current of nitrogen. Now we have known for a long time that such a current carries with it much carbonic acid.

As for Experiment DLVIII in which I found 2% of oxygen, that is the one in which the apparatus exploded, and in which the animal, which was killed instantly, had not consumed the slight excess of oxygen which had been liberated in its blood.

At any rate, most of the free gas is made up of nitrogen, and from this fact a very serious danger results; for carbonic acid and even oxygen might be redissolved rapidly, and Nysten [2] long ago demonstrated that their presence in the venous system is not dangerous, unless enormous quantities, especially of carbonic acid, are introduced. It is true that in our experiments there is gas in the arterial system itself.

It is probable that all the excess nitrogen thus passes to the gaseous state. Now we have seen that at 10 atmospheres there are about 8 cubic centimeters of nitrogen in excess in 100 cubic centimeters of blood. Supposing that a dog weighing 14 kilograms contains 1 kilogram of blood, we find that there may be liberated in the arterial and venous vessels 80 cubic centimeters of nitrogen, bringing with them about 20 cubic centimeters of carbonic acid; that is sufficient to bring on symptoms that are immediately fatal.

Now we can picture the effects of sudden decompression. Let us first represent things as bad as possible; let us suppose an animal brought in 2 or 3 minutes from 10 atmospheres to normal pressure. Immediately, in the whole vascular system, gases escape in abundance; there is frothy blood in the veins, in the arteries, in the portal system, even in the vessels of the placenta and the foetuses,

when the animal was pregnant (Exp. DXXXVI). The heart, which continues to beat for a few minutes more, pumps into the arteries the gases which its left cavities contained, although they are rarely found there; the course of the venous blood, which continues a little while, brings to the right cavities tiny bubbles of gas which collect there in such quantity that a cat (Exp. DLXX) furnished me with 33 cubic centimeters of it, and a little blood freed of gaseous bubbles proceeds to the left heart by some of the pulmonary arteries. The others are obstructed by the foam sent out by the right heart. We find here the effects of this difficulty which gases have in passing through the capillaries, difficulties which so often cause the injections of anatomists to fail: we see bubbles of gas refusing to pass through the lungs, and in certain experiments we have seen the mesenteric arteries full of bubbles of gas without the blood of the portal vein containing any.

Let us suppose now the lightest case, either of an animal decompressed from only 6 atmospheres (Exp. DXXX), or, beginning with 10 atmospheres, of one decompressed very slowly (Exp. DLXXI, DLXXVI, and DLXXVII). In these cases, bubbles of gas will be liberated, though smaller and much less numerous; those of the venous system will stop in the lungs, and will cause some respiratory difficulties; then when they have been agitated and made extremely small (one sometimes needs the microscope to see them), they will reach the left heart and thence be pumped into the arteries, where they will join those which spontaneously developed there and which the circulation has not yet driven into the veins. It may be that they will finally be redissolved without causing any very definite symptoms; but if, unfortunately, some of them, drawn by the circulation into the capillaries of the nervous system, check locally the course of the blood there, immediately, instantaneously, as in the experiment of Sténon, a paralysis or a local excitation is the result; only in the case in point, the bubble is so small that it soon disappears and everything returns to the normal state.

We understand that between these two extremes there must lie many intermediary cases, and the experiments reported above present plenty of examples. Nothing is more startling than to see animals decompressed from 6 to 8 atmospheres leaping out of the apparatus, as if delighted with their liberty, then seized after a few minutes by a paralysis which always begins in the lower limbs, but which often invades next all the rest of the body.

Another surprising thing is this interval of 5 to 10 and even 15

minutes which almost always elapses between the moment of decompression and that of paralysis, either because the gas does not escape immediately in the whole body, or because a certain time is needed for the bubbles of air to cut off the medullary circulation.

It is no less strange to see, in certain experiments, for instance DLXXV, life persisting for hours when the almost general paralysis of the animal left free only the movements of the diaphragm, and gurgling could be heard in the heart, revealing at the beginning the presence of a great quantity of gas in the right heart and the lungs.

In this case, the animal is slowly asphyxiated, as is proved by the increasing darkness of the blood flowing in its arteries. It is evident that the pulmonary output is insufficient to provide an adequate quantity of oxygenated blood in the arteries.

If now we ask why the nitrogen thus liberated is not finally redissolved in the blood, or why it does not escape through the lungs, the reply is easy.

As a matter of fact, the blood circulating through the vessels under normal conditions is almost saturated with nitrogen through the respiration of air; when arterial blood is shaken with air, it can be made to absorb only some tenths of a cubic centimeter of nitrogen more than it already contained. There is no reason then why the excess which has been liberated should be redissolved. Now the free nitrogen does not escape through the lungs because it is in an atmosphere which is four-fifths nitrogen, and nothing urges it out.

Continuing this reasoning, we begin to think that there might be an advantage in causing the animal to inhale pure oxygen or a mixture of oxygen and hydrogen, to stimulate at the same time the dissolving of the nitrogen in the blood and its diffusion through the pulmonary membranes. And this I did with some success in the experiments which I shall report later.

Finally, a third strange fact, the paralysis always began in the hindquarters (except in Experiment DLXII). Why is this place selected? Is it a sufficient explanation to say: the lumbar region of the spinal cord is the part which works hardest when the animal jumps and runs? I merely remind the reader that paraplegia is also the most frequent symptom in divers and workmen in caissons.

When death occurs shortly after the beginning of the paralysis, it is evidently under the influence of the same cause as the paralysis; the bubbles of gas, after cutting off the circulation in the lumbar

enlargement, check it in higher points (where autopsy finds them) until finally respiration ceases; during this time, besides, the pulmonary arteries are filled with free gases; asphyxia comes everywhere at the same time.

But it has happened sometimes that the paralysis was localized in the lower limbs, or at least has made only rather slow ascending progress; so that death occurred only after several days (Exp. DXXIV, DXXVI, DXXXIV). If we consider the lack of care for the animals, we may think that some might survive, though paralyzed, as happens to some divers.

At death, there was found, as we have already noted, a more or less extensive softening, in the midst of which bubbles of gas (Exp. DXXVI) were sometimes seen even after 4 days, and which were surrounded by the inflammatory processes which had caused death. I call attention to the rapidity with which a softening occurred so great that the spinal marrow was liquid like cream; in Experiment DXXIV, it was less than 24 hours.

I shall only mention to the reader the remarkable physiological symptoms which accompany these interruptions of the medullary circulation and the following changes in metabolism. Those who have had the patience to read the preceding experiments must have noted the strange occurrences of an emission of bloody urine and sperm, of contraction of the limbs, of constriction with exaggerated reflex movements of the anal and bladder sphincters, of sensitivity retained after the loss of motility, etc. I shall only recall here the curious point of the afferent and efferent conductivity of the sciatic nerve, so much affected by the change in the corresponding region of the spinal cord (Exp. DXXXIV). I consider that these softenings produced experimentally might contribute greatly to the progress of the physiology of the spinal cord, and render useful services to the medical diagnostician: it is a mine to be worked which would be as prolific as the one which gave so many useful results in the skillful hands of Professor Charcot.

Some of the experiments reported above show that the presence of bubbles of gas in the blood is not a necessary cause of death or even of symptoms manifest to the eyes of the observer. Thus in Experiment DXXXIX, in which the pressure was 3½ atmospheres, from the blood received under mercury in a test tube very small bubbles of gas escaped, and yet the animal, decompressed in 1 minute, did not seem at all affected. Looking very closely and using a magnifying glass, I even saw in one case (Exp. CLXXXIV)

the bubbles of free gases escaping under mercury from the blood of a dog placed at 3 atmospheres.

It is evident that in the dog of Experiment DXXXIX, which was some days afterwards decompressed from 5 atmospheres without symptoms, the blood in circulation contained fine bubbles. But they could pass through the capillaries without obstructing the circulation, and probably were dissolved more or less rapidly.

The presence of such bubbles would be enough, I think, even if there were no stoppage of the circulation, to explain, on the basis of irritation of the tissues, the slight symptoms of workmen in caissons, the "puces" (fleas) and the "moutons" (sheep), discussed in the historical part. We therefore understand the risks run by these workmen, whose paralysis or death at these limits depends upon the size of a bubble of gas. It is not surprising then that symptoms, slight in some and fatal in others, appeared after too sudden decompression from about 4 atmospheres.

But the presence of bubbles of nitrogen in the blood, irritating the tissues in contact with them, when they are small enough to traverse the capillaries, or causing more serious and more lasting symptoms, when they interrupt the circulation, does not constitute the only danger to which animals rapidly decompressed are exposed, nor is it perhaps the most dangerous.

Indeed, the very tissues of the organism, which are impregnated with liquid, and the liquids other than the blood are laden with a growing proportion of nitrogen, from contact with the blood which is supersaturated with it. And when the decompression occcurs, these gases must necessarily return to a free state, distending and even lacerating the tissues from which they escape. Experiments DXXXVI, DLVIII, DLIX, DLX, and DLXIII have shown us gases in the subcutaneous or intermuscular tissue, in the liquids of the eye, in the cerebro-spinal liquid, in the spinal cord, etc. Experiment DLVIII, in which the explosion took place, is quite remarkable in this reference; the subcutaneous emphysema was such that the dog had become absolutely cylindrical. Let us mention particularly also Experiment DXXXVI, in which in a pregnant bitch we found gas not only in the blood vessels and tissues of the animal, but also in those of the foetuses, and even in the allantoid liquid; the amnion, which is much less vascular, contained none.

These gases, imprisoned in the meshes of the tissues, must, when they do not cause death, be the cause of pains and local swellings, and it is evidently to them that we must ascribe the muscular

swellings, the swelling of the breasts, etc., of which we have given several examples in the chapter devoted to history.

In summary, sudden decompression causes many more or less severe symptoms, all of which are easily explained by the liberation in the blood plasma as well as in the interior of the tissues, of the nitrogen which was dissolved in excess under the influence of the pressure.

I admit that, in this collection of data which, although infinite in variety, still has a single simple cause, one point still surprises me. I cannot understand why, in certain dogs subjected to high pressure, the blood extracted from the vessels did not contain free gases: for instance, in Experiments DXLVI and DLVI, in which the pressure was 6½ and 8 atmospheres. Experiment DLXIII is particularly interesting in this connection: the dog, decompressed after a long stay at 6 atmospheres, was paralyzed, and yet no free gas appeared in its blood; but the symptoms having grown more serious, gas was found after death not only in the blood but also in various organs, and particularly in the spinal cord: this was probably the cause of the immediate paralysis.

It was also somewhat difficult at first to understand why dogs suddenly decompressed from 5 or 6 atmospheres, rabbits from 6, 7, 8, and sparrows from 8, 9, 10, did not die, and did not even show any symptoms, though they certainly had free gases in the blood, since I sometimes observed the presence of gas in an experimental animal, as in Experiments DXXXIX and DLXIV. I think that this apparent anomaly should be explained by the fact that the escape of bubbles which were very small at the time permitted them to pass without hindrance through the system of capillaries and to gather in the venous system. Now if all the gas thus set free is collected in the veins, it cannot constitute a serious danger for the animal.

Let us consider again a calculation which we have already made. At 5 atmospheres, for example, Table XII shows that a dog has an average of 6 volumes of nitrogen per 100 volumes of blood, that is, about 4 volumes more than the blood can dissolve at normal pressure. Let us take a dog weighing 10 kilos, and let us suppose that it has in its blood and lymph vessels 1 liter of liquid; there will be 40 cc. of nitrogen, with about 10 cc. of CO_2 which, as a maximum, will collect in the hollows of the right heart. This collection will be made progressively, for it is well known that in a liquid supersaturated with gases by pressure, the gases will not escape instantaneously at the time of the decompression.

Now the 10 cc. of carbonic acid will be dissolved again or will be given off at once by the lungs; as for the 40 cc. of nitrogen, which corresponds to what would be present in 50 cc. of air, we know that although such a volume of air, injected suddenly into a vein of the heart, can check the contractions of this organ, especially when this air is cold, one can, on the contrary, introduce without harm into the circulatory channels much larger quantities of air, if moderate and successive injections are made.

Nysten[1] long ago demonstrated this fact; but since misapprehensions on this point are still common, I think I should report a few very convincing experiments in this connection:

Experiment DLXXXII. February 24. Little dog, weighing 4 kilos, sick. Injected into the jugular vein in 4 minutes 14 cc. of air. The animal dies in 10 minutes.

Bloody foam in the right heart and the pulmonary artery; no gas in the left heart.

Experiment DLXXXIII. July 25. Dog weighing 5 kilos. Outer temperature 21°.

At 3 o'clock, single injection in the left femoral vein of 20 cc. of air.

Immediately the heart is heard to beat with the noise of a dry sponge being squeezed under water. The animal ceases to breathe; the heart seems to stop; the conjunctiva, but not the cornea, becomes insensible.

Then the respirations begin again, at first very rare and very deep, then hasty. The heart sounds reappear, normal.

3:15; new injection of 20 cc. Same phenomena, although less pronounced: sensitivity, respiration, heart beats do not completely disappear; stiffenings of the front legs; little cries.

3:25; the animal seems quite recovered. Injection at one time of 40 cc. of air. Immediately stiffenings of the legs, heart sounds respiratory difficulties; the whole condition becomes worse, and at 3:35 the heart can no longer be heard.

Autopsy at 3:50. Right auricle and ventricle full of blood frothed with air, with clots full of air; a little gas in the vena cava. No air in the pulmonary arteries or the left heart.

Experiment DLXXXIV. February 14. Bulldog weighing 12 kilos.

Progressive injection in 9 minutes of 130 cc. of air, into the left jugular vein.

Seems rather uneasy during the injection, but released immediately after, is in good condition.

Experiment DLXXXV. February 24. Vigorous hunting dog, weighing 15.5 kilos. Outside temperature 14°.

3:15. Every two minutes, an injection of 65 cc. of air in 30 seconds into the right jugular vein, with an excellent glass syringe.

At each injection the animal moans, and immediately, even at a distance, the sounds of heart gurgles are heard.

After the 10th injection (650 cc.), the animal does not seem to be in danger. At the 24th minute, injections are resumed, but this time every minute.

After the 17th injection (1100 cc.), the animal groans, urinates, stretches out its legs with force. The heart beats grow slow, the respirations are very rare, and the animal dies at 3:55. Its temperature dropped 1°.

I found the right heart full of foam, blood frothed with air, with a large quantity of free air; it was present also in the venae cavae and the pulmonary arteries.

Numerous bubbles of air in the left heart and the cardiac *arteries* and veins; there was none in the arteries of the limbs and the portal vein.

In Experiment DLXXXII, a dog, which was small, it is true, and sick, was killed by an injection of 14 cc. of air, while in Experiment DLXXXV, it was necessary to go as high as 1100 cc. to kill a large dog. These experiments, in short, show us as many differences for artificial injections of air into the veins as for the sort of physiological injection which takes place during sudden decompression.

One of the most important elements to be considered in regard to the appearance of morbid symptoms following decompression is the length of the stay in the compressed air. This plays the principal part, after the degree of compression and the speed of the decompression. So, whereas for dogs decompressed immediately after the desired degree had been reached there are no serious symptoms, as Table XVIII shows, before reaching 7 atmospheres, in Experiment DLXIII, we see a dog dying quite rapidly after leaving the apparatus in which the pressure of 6 atmospheres had been maintained for 3½ hours. Experiment DXV made on a sparrow is still more remarkable. However, Experiment DLXIV shows us a dog which had no symptoms after a stay of 4 hours under 5½ atmospheres; but he had in his blood abundant bubbles of gas, and was consequently under the threat of an imminent morbid attack.

In conclusion, it is possibly interesting to note that aquatic animals are killed by sudden decompression for the same cause as terrestrial animals and by the same mechanism. But it will no doubt seem enough to report one experiment to support this statement which presents true interest in regard to the conditions of life of these creatures:

Experiment DLXXXVI. April 6. Eels "de la montée" (young), transparent, subjected for two days to a pressure of 10 atmospheres of air.

2 o'clock, decompressed suddenly; emit from their mouths bubbles of gas.

6 o'clock, all dead; the hearts, which are full of air, can be seen beating; because of the transparency, bubbles of gas can be seen in all the vessels.

Subchapter IV

PROPHYLAXIS AND TREATMENT OF SYMPTOMS OF SUDDEN DECOMPRESSION

Considering these dangerous symptoms, a double question is naturally suggested: how to prevent them, and how to cure them.

They will be prevented, as common sense suggests and experience proves, by making the decompression slow enough. On this point the experiments summarized in Table XIX give very clear indications. We see, for example, that from 10 atmospheres on, we avoided serious symptoms by giving more than 1 hour and 10 minutes to the decompression (Experiments DLXXI, DLXXII, DLXXVII, DLXXVIII). But this is the minimum time, since an hour, in Experiment DLXXIV, did not prevent death. I set aside Experiments DLXXX and DLXXXI, which show a peculiarity that I still cannot explain.

I did not perceive great differences between the cases in which the decompression was made continuously at the rate of 8 minutes per atmosphere (Exp. DLXXVIII), or 10 minutes (Exp. DLXXVI), and those in which it was made by sudden drops with intervals of rest (Exp. DLXXII, DLXXVII). Besides, the data are not numerous enough to permit conclusions in favor of either of these methods.

But it is certain that beginning with 10 atmospheres one cannot be sure that a dog will be out of danger unless the decompression is given a duration of at least 12 minutes per atmosphere. We shall return to these data in the third part of this work.

And now for the second question. The decompression was made too quickly. Gases escape into the blood, which obstruct certain vessels and threaten the experimental animal with death. Evidently I should have thought of causing them to be redissolved by subjecting the animal to a new compression with the purpose of decompressing him with controlled slowness. And that is what I did in the two following cases:

Experiment DLXXXVII. October 18. Dog of Experiment DXXXVIII. It is paraplegic as a consequence of a sudden decompression from 7 atmospheres; the paraplegia began at 3:21.

From 3:25 to 4:05 was taken again to 7 atmospheres, and kept there until 4:12. Then decompressed slowly; normal pressure was reestablished at 6 o'clock.

On leaving the apparatus, the animal is still paralyzed in the hindquarters, or rather, its hind legs, stiff and contracted, no longer are controlled by the will; sensitivity remains, and we obtain reflex movements by pinching, but very slowly.

Dies during the night.

Experiment DLXXXVIII. October 16. Dog of Experiment DXXXVII.

Paraplegic and stiff since 2 o'clock, as a consequence of a decompression from 7 atmospheres. Recompressed to 7 atmospheres from 2:15 to 3:02, then decompressed in an hour.

The animal seems better and calmer; but it is still paraplegic though not stiff; the temperature of the hind legs has risen.

Dies the next day.

No gas is found in the vessels; but the spinal cord presents, from the lumbar enlargement to the middle of the dorsal region, little bloody spots scattered in the antero-lateral fasciculi. There is no softening.

I did not multiply these experiments; it is evident that the recompression was managed here too slowly for it to be possible to draw any conclusion from these results. However, I do not doubt the effectiveness of this method, on condition that one could obtain a very rapid recompression. We saw in the historical part that it was already used by workmen and recommended by the physicians who had attended them.

The considerations already presented (Page 884) had put me on the track of a quite different method, which aimed not at redissolving the bubbles of free gases in the blood, but at forcing them to escape through the respiration.

These bubbles are composed, I have said, of nitrogen; when they reached the pulmonary capillaries, there is not much likelihood that they will be diffused and mingle with the air of the lungs, because that air also is four-fifths composed of nitrogen. Considering this, I thought that if the animal were caused to breathe a gas containing no nitrogen, pure oxygen, for example, the diffusion would take place much more rapidly, and perhaps would even be rapid enough to cause all the gas to disappear from the blood, and thus save the animal. I give here the results of some experiments performed in this way:

Experiment DLXXXIX. October 31. Dog of Experiment DXLIII.

Decompressed from 7¼ atmospheres, lying down, very sick since 2:15, with gurgling in the heart.

At 2:20, pure oxygen administered to him continuously.

At 2:30, the sound of gurgling has ceased, respiration is freer,

the animal tries to rise using its front feet; its eyes are no longer wild.

At 4:30, use of oxygen discontinued. The animal is quite recovered in regard to respiration and heart.

But it is still paralyzed, or at least cannot stand up on its feet, although it moves its limbs and head spontaneously.

Found dead the next day. No gas in the heart or the vessels.

Experiment DXC. November 12. Dog of Experiment DXLV.

3:12. Decompressed from 7¼ atmospheres, paralyzed, with loud gurgles in the heart, and great respiratory difficulties.

3:20. We begin administering pure oxygen.

3:35. The respirations are very deep and frequent; there are no sounds of heart gurgles. The animal makes general movements, and tries to take off the muzzle with its paws.

The respirations become regular for a certain time, then they decrease in intensity, and about 4:30, it is clear that the animal is becoming exhausted and is going to die.

It is opened at 4:45, when about dead. No gas in the veins or heart.

Experiment DXCI. November 25. Bitch of Experiment DXLVII.

Decompressed from 7½ atmospheres, paralyzed at 3:23, gurgles, lack of sensitivity, etc.

3:28. Since the respiration has stopped, we are obliged to give artificial respiration with oxygen. After 6 to 7 artificial respirations, spontaneous movements return, the heart begins to beat distinctly, the gurgles diminish, insensibility disappears.

But at this moment the supply of oxygen fails and we cannot continue the experiment; the animal dies almost immediately afterwards.

We find the right heart much distended with blood, with only a little foam.

Experiment DXCII. November 27. Dog of Experiment DXLVIII.

Paralyzed, very loud gurgles, decompressed from 7 atmospheres. At the moment when oxygen inhalation has begun, the heart gurgles seem to increase a little, then the heart almost completely ceases to beat; gradually it becomes quite strong and frequent. But gas does not cease escaping from the upper end of the jugular vein, which has been exposed, and the animal dies after a half-hour.

Blood very red, and without gas in the left heart; blood fairly red with tiny bubbles in the right heart.

Experiment DXCIII. December 6. Dog of Experiment DL.

Decompressed from 7½ atmospheres at 3:22. Immediately paraplegic, front legs a little stiffened, but pulling back when pinched; hind legs stiff and insensible; very loud gurgles.

I give oxygen inhalations and expose its jugular vein, which is full of gas.

Immediately the respirations grow regular; little by little the gas bubbles become smaller in the jugular, sensitivity returns a little to the hind legs; the animal is evidently better.

About 5 o'clock, the gases have completely disappeared from the jugular, the animal raises its head when called by a whistle. The oxygen inhalations are continued until 9 o'clock in the evening.

December 10. Is no longer completely paralyzed in the hindquarters; can stand up and drags its feet on the back of its toes when walking. Exaggerated sensitivity in the hind legs. Disposition becomes bad.

December 11. Lying down, paralyzed; slight reflex movements of the hindquarters. Very much exaggerated sensitivity in the front legs. Rectal temperature 37.9°.

December 12. Dies.

Nothing noteworthy in the thoracic and abdominal viscera.

No medullary softening. Cross sections of the spinal cord show in the white and the gray substances red dots which diminish progressively from the lumbar region to the cervical region.

Experiment DXCIV. December 11. Dog.

Compressed to 8 atmospheres. Decompressed very slowly to 7¾. Then in 3 minutes to normal pressure; 5:15.

The animal is withdrawn immediately and given oxygen inhalations.

5:25. Pulse 120; the rectal temperature, which before the experiment was 38.5°, is 37.5°. Respiration regular; bubbles of gas are visible in the jugular, which has been exposed.

5:30. Placed on the floor a moment; is paraplegic.

5:50. Pulse 90; there have been no gurgles in the heart; no more gas is seen in the jugular; temperature 37.2°.

6:15. Use of oxygen discontinued; placed on the floor; is no longer paralyzed, and drags the left hind foot on the toes only a little; the hind legs seem insensible.

It is affected by a peculiarity of movement which makes it turn to the right; its head is bent strongly towards the right, its eyes turn in the same way. It has strong nystagmus and quiverings of the neck muscles. When it wants to walk, it takes many precautions, then at the least obstacle it falls, turning on its right side.

6:30. Manifest improvement; the hind legs and the tail are sensitive; the animal walks much better and appears intelligent.

6:45. The improvement does not continue; the animal again drags its left foot.

December 12. More paralyzed than the day before, can hardly walk, and still turns towards the right.

Stimulus of the hind legs causes energetic reflex movements; but the dog does not seem to notice it. The hind legs, especially the left, are warmer than the others.

December 14. Still paraplegic, cannot stand up even an instant.

December 18. Same condition; urinates easily; energetic reflex movements.

Experiment DXCV. December 13. Dog.

Taken to 8¼ atmospheres; decompressed in 3 minutes. Immediately, at 3 o'clock, oxygen administered.

It is not paralyzed; but after some minutes, paraplegia begins and becomes complete, with reflex movements persisting.

No gurgles in the heart heard at all, and respiration goes on fairly well.

4:50. Oxygen discontinued. The animal cannot stand on its hind legs.

Respiration maintained well, heart beats are unaltered.

6:30. Same condition; sensitivity in the hind legs dulled.

December 14. Lying down, cannot stand on its hind legs, although it can move them spontaneously, and perceives pricks in them. Dies during the night of December 14-15.

The data which have just been reported, and the results of which had already been listed in Table XVIII, show that one of our anticipations was completely realized. Under the effect of inhalation of pure oxygen, the gases contained in the veins and the right heart diminished, then disappeared; the heart gurgles either did not appear or stopped when the respiration of oxygen began early. The danger of an immediate death, through stoppage of the pulmonary circulation, was therefore averted.[4]

But yet we could not save our animals; the paralysis persisted, and in spite of a real immediate improvement, ended in carrying off our experimental subjects.

That is because the inhalation of oxygen could not bring back into the blood stream and dispose of the bubbles of gas which had stopped here and there in the capillaries of the central nervous system. And it could not, for an even better reason, cause the absorption of the bubbles which, as we have seen, escape into the interior of the tissues.

Upon them, only recompression can have a beneficial effect. But, on the other hand, recompression cannot cause a considerable collection of gases in the right heart to be redissolved.

We are, therefore, led to recommend the successive use of the respiration of oxygen, to eliminate the nitrogen stored up in the right heart, and recompression to dissolve the bubbles which have stopped in the capillaries or are scattered through the tissues.

Even so, we cannot be sure of a cure, because the bubbles of gas, when they pass to a free state in the interior of delicate tissues, like those of the spinal cord, may have caused disturbances or lacerations there, the fatal effects of which cannot be averted by the disappearance of the bubbles.

It is, then, upon preventive measures, that is, slow decompression, that industry must depend, and that is a point to which we shall return in our third part.

Subchapter V

SUMMARY

In summary, sudden decompression, beginning with several atmospheres, brings on symptoms of varying severity depending upon the degree of compression, the speed of the decompression, the animal species, the individuals, and the state of the experimental animal at the time.

These symptoms must be attributed to the escape of nitrogen which had been stored up in excess in the organism, following Dalton's law.

This gas changes to a free state in the blood vessels, the different organic liquids, and even the interior of the tissues; it may therefore, according to circumstances, check the pulmonary circulation, soften and cause anemia in certain regions of the nervous centers and especially the lumbar enlargement of the spinal cord, lacerate the tissues, and produce swellings or a more or less extensive emphysema. The severity of the symptoms depends upon both the seat and the extent of these multiple disorders.

A controlled decompression of 12 minutes per atmosphere is necessary to prevent these symptoms in dogs, when the compression has risen to about 10 atmospheres.

A recompression, either immediate or following the inhalation of oxygen in case heart gurgles are observed, is the only means of combatting successfully the symptoms of decompression.

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[1] At 3 atmospheres, gas escapes in the syringe from the blood drawn.

[2] *Recherches de physiologie et de chimie physiologique.* Paris ,1811, p. 55 and 81.

[3] *Loc. cit.*, p. 15 et seq.

[4] Consequently the inhalation of oxygen would be an effective means of checking the effects of the introduction of air into the veins. With this in view, I have made a number of experiments quite encouraging for surgeons.

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PATHOGENETIC FACTORS AND PATHOLOGICAL CONSEQUENCES OF DECOMPRESSION SICKNESS

H. R. CATCHPOLE AND ISODORE GERSH[1]

Naval Medical Research Institute, Bethesda, Md., and Dept. of Anatomy, The Johns Hopkins University, Baltimore, Md.

For almost fifty years no comprehensive review of the pathological consequences of decompression sickness has appeared. The reviews of Paul Bert (1878) and of Heller, Mager and von Schrotter (1900) defined the etiology of the disease and formulated the main aspects of its pathological results. The views of these authors have remained essentially unchallenged. But since that time a great clarification of the physical factors involved in aeroembolism has come about and a need has arisen to integrate more recent work in pathology with the older literature, with the objective of reinterpreting both in terms of these physical factors.

In dealing with this literature, key references have been preferred to exhaustive quotation. Deliberate limitations in subject matter have caused the exclusion from discussion of changes referable to the air-containing cavities, where air expansion *per se* gives rise to the pathological effect (pain, rupture, hemorrhage); thus removed from consideration are: aero-otitis media, sinus pain, pain and other effects arising from trapped gases in the intestinal tract, and, as possibly connected with the same phenomenon, pain associated with the teeth (86, 114, 129).

Some of these factors as pertaining to aviation have been dealt with by Armstrong (1). Also excluded are considerations of pathological physiological changes, e.g., in renal, cardiac and metabolic functions, in the gastro-intestinal tract, in the composition of the blood, in blood vessels and in the general phenomenon of shock. Effects due to anesthesia have been omitted, but a section on drugs and exercise is included. Effects directly referable to acute and chronic anoxia have also been omitted. In so doing, an effort has been made to separate the results of low oxygen on the body as a whole from those traceable to aeroembolism.

This review falls into two sections. In the first, physical and mathematical considerations governing the uptake and elimination of gases by the body and by individual tissues are discussed, and the conditions are defined for the relative susceptibility of a given site to bubble formation. In the second section, the gross and microscopical pathology of organs and tissues following decompression are related to these factors. While the effects of pressure and those of altitude are usually considered separately, the three categories of caisson disease, decompression sickness of divers, and aeroembolism of aviators, are regarded as basically similar entities, in which pathological differences are, or will prove to be, adequately explained by reference to the physical factors involved.

[1] Present address: Department of Pathology, University of Illinois, College of Medicine, Chicago, Ill.

PATHOGENETIC FACTORS IN DECOMPRESSION SICKNESS. *Physical Considerations. Mathematical principles.* The phenomena accompanying gas bubble evolution in the bodies of animals subjected to decompression have led recently to a revival of interest in the purely physical mechanisms involved in the separation of a gaseous phase from a saturated or supersaturated solution of a gas. This topic had already been explored in the eighteen seventies (for early literature, see 38, 72). The conditions for stability of a bubble of gas immersed in a liquid saturated with gas at 1 atmosphere have been defined (38, 72, 102) by the relation:

$$P = H + 2\sigma/r$$

where P = pressure in the bubble in excess of atmospheric, H = the hydrostatic pressure at the bubble level, σ = surface tension of the liquid, r = radius of the bubble.

As the radius r of the bubble diminishes, the second term of the above expression gets larger, and when r approaches the dimensions of a water molecule, the excess pressure due to the surface tension of the liquid is counted in thousands of atmospheres (38). There exists, in fact, a lower critical value for r (that is, a minimum bubble size) below which this excess pressure will literally squeeze the gas back into solution (72, 102, 128). Above the minimum size, however, the bubble will grow by diffusion as long as the tension of dissolved gas in its vicinity is greater than the gas tension in the bubble. For a free bubble to arise *de novo* it is necessary that this minimal size be achieved by sufficient molecules simultaneously attaining enough energy to overcome the forces of attraction between them. This was considered to be within the realms of statistical probability by Piccard (128). However, other theoretical treatments and experimental work reported by Dean (38) and Harvey (72) lead to the conclusion that bubbles do not tend to form in liquids spontaneously unless high negative pressures or considerable degrees of superheat are applied.

Gas masses existing in cracks or attached to irregular surfaces, on the other hand, have very different conditions for stability depending on the geometry of the surface, the shape of the gas-liquid-solid junction, contact angles, surface tension and ΔP (see below) which have been worked out for certain situations (72). Such gas masses may be stable at or below a critical size, but they grow indefinitely by diffusion above this critical size; an important property is that their gas content may be increased gradually by successive boostings. Gas nuclei are defined (72) as small invisible masses of gas usually, but not always, attached to a surface, which grow by inward diffusion of gas from the surrounding liquids. These enlarged masses may eventually become detached as free bubbles, or bubbles may become detached leaving behind a nucleus for the growth of other bubbles. The origin of these gas collections is obscure. The condition that they normally be attached to a surface, or contained in a crack, arises from the instability of small free bubbles noted above. Gas monolayers are believed not to promote bubble formation, but the possibility that multilayers of gas may act as nuclei has been suggested (38). Hydrophobic surfaces hold gases very tenaciously (72) but there is no evidence that tissue surfaces possess such properties.

Gas nuclei may be produced in surface cracks or acute angled cavities by statistical fluctuations of gas molecules (72, cf. also 128).

Harvey (71, 72) has introduced a useful expression to define the tendency, ΔP, of a gas to leave a liquid phase:

$$\Delta P = t - P$$

where t = gas tension in the liquid; P = hydrostatic pressure (this may be positive or negative in sign; the latter condition obtains when a pull is exerted on a liquid). Bubbles may form *de novo* when a very high negative pressure is produced in a liquid (when P is negative, ΔP increases). Acting in the vicinity of a gas nucleus, local negative pressures will favor the diffusion of gases into the nucleus. Such "cavitation" of a liquid may arise through pressure pulses, sound waves, Bernoulli effects (motion of liquids through constricted tubes), turbulent motion and through stretching. Increase of t will produce the same effect by providing a richer population of gas molecules for diffusion. Dean (38) attributed most cases of bubble formation in liquids in motion to vortices produced by turbulent flow. However, the streamlining of the vascular flow militates against this view as applied to bubble formation in animals (72).

Models of systems containing gas nuclei were studied by Pease et al. (126). Capric acid (M. P. 31°C) cooled to the point of crystallization provided foci for cavitation in aqueous solutions, and the process was reversed on warming; i.e., gas nuclei were apparently created and destroyed by these procedures. The same authors found that stearate monolayers on glass promoted cavitation; alcohols, amino acids and proteins abolished this effect. Removal of gas nuclei from liquids was early described by Tomlinson (cited by Dean, 38), and since that time bubble nuclei have been variously removed by boiling or partial evacuation of water, followed by standing (38); by centrifugalizing, filtering, boiling or subjecting to 1000 atmospheres pressure (72); and by pressure, evacuation or chemical agents (126). The remarkable properties of liquids freed from gas nuclei in resisting superheat and negative pressures have been frequently described (72, 97, 98). Harvey et al. (73) distinguished between macronuclei, removable from water by centrifugalization, and micronuclei, removable only by high pressures (1090 atmospheres). Freshly drawn blood is completely free of macro- and micronuclei; such nuclei are neither present in the blood plasma, nor attached to formed elements or to any other constituent of the blood. It must therefore be assumed that they are attached to the linings of blood vessels, and that bubbles formed at the sites of the nuclei are released into the circulation (72).

Factors in the growth of gas nuclei in the body. If the concept of $\Delta P = t - P$ be adopted as a measure of the bubble forming tendency, and the presence of gas nuclei in the body be accepted, a number of conditions favoring, or tending to prevent, bubble formation become intelligible. Local production of CO_2 increases t and therefore increases ΔP, and so conduces to bubble appearance (69, 110); muscular activity, besides increasing the CO_2 tension locally gives rise to mechanical tensions and to consequent decrease in P; for both reasons it favors

bubble formation (28, 68, 110, 177). Tissue manipulation of almost any kind (stretching, cutting, crushing) leads to the same result (73). Bone fractures are a potent site of bubble formation (17, 70), since they lead to sharp momentary falls in the value of P. Bubbles form more readily in veins (low P) than in arteries (high P) (72, 177). Among factors delaying or preventing bubble formation in cats stimulated to muscular activity at altitude were: pre-stimulation (109, 177), anoxia (109, 69), traumatization of legs by skinning (109); these treatments promote local hyperemia or hyperventilation, and result generally in an increased value for P combined with faster elimination of nitrogen. Not susceptible of such simple analysis are the effects of vasoconstriction, which are equivocal, and of vasodilatation (aminophyllin), which are negative (137). It is evident that for the body as a whole, ΔP represents an aggregate of pressure differences of constantly varying magnitude in different sites. The situation is summarized by Harvey (72): "at ground level ΔP is nearly zero in tissues to negative in arteries. On rapid ascent to high altitude it is at first positive everywhere, but quickly becomes negative in arteries (due to blood pressure and rapid equilibration with alveolar air), remaining locally high in small vessels (due to CO_2 and N_2 of tissues) for a time, finally becoming zero to negative except for regions of fat deposits or very poor circulation."

Establishment of critical pressure differences. Decompression establishes ΔP values necessary for bubbles to grow. Boycott, Damant and Haldane (21) found experimentally in goats and man that decompression from 2.3 atmospheres to one atmosphere never produced symptoms. On the basis of equivalent gas volumes they argued that a drop of approximately one-half of the original gas pressure would be safe whatever its value (e.g., from 4 to 2 atmospheres, from 6 to 3 atmospheres, etc.). But as will be seen in a succeeding section, this assumption is untenable, and Haldane himself (65) has stated that above six atmospheres it is no longer quite safe to halve the initial pressure. Behnke (5) proceeded on the basis that the difference between tissue gas pressure and the external pressure should at no time exceed 1.3 atmospheres (2.3 minus 1.0 atmosphere). He then calculated decompression rates that would hold the external pressure at not more than 15 lb/sq. in. below the greatest tissue pressure. The views of both Haldane and Behnke have been critically examined by de Burgh Daly and his associates (37, 43). Smaller animals appear to be able to tolerate greater pressure differentials. Guinea pigs survive decompression from 60 lb/sq. in. (gauge) to atmospheric pressure (15 lb/sq.in.), and bubbles are produced with difficulty in rats and mice.

For the occurrence of aeroembolism in man there appears to be a critical altitude of 20,000 to 25,000 feet (0.45 to 0.37 atmosphere) as given by the British authorities (133), or perhaps somewhat higher. Under extreme conditions of stimulation, bubbles appear in cats decompressed to 35,000 feet (0.23 atmosphere). In rabbits, bubbles can not usually be produced at 40,000 feet (0.18 atmosphere); at 45,000 feet they are formed under specified conditions (27). Bubbles scarcely appear in quiet frogs below 60,000 feet, although violent mus-

cular activity reduces the ceiling considerably (177). The smaller rodents again are relatively refractory to bubble formation and rats at altitude, in a state of normal activity, do not yield bubbles at 50,000 feet (177).

Effect of rate of decompression. Since the time of Paul Bert, it has been repeatedly demonstrated that the severity of decompression sickness is directly related to the rate of decompression. Altitude studies by Griffin et al. (62) compared the effect of different rates of ascent (1000 and 5000 ft. per minute) and showed a markedly greater susceptibility to bends after the faster ascents.

Systematic studies on rabbits decompressed to altitude showed a relation of rate of decompression to the incidence and severity of bubble formation (table 1) (27). When decompressed to 45,000 feet in eight minutes or less, mortality was high, and survival time became progressively shorter as the time to altitude decreased. At decompression times exceeding ten minutes to reach 45,000 feet, mortality was low and bubble incidence minimal or zero.

TABLE 1

Effect of rate of decompression on the 50 per cent survival time, the percentage of deaths, and the symptoms of rabbits decompressed to 45,000 ft.

RATE OF DECOMPRESSION	50 PER CENT SURVIVAL TIME	PERCENTAGE OF DEATHS	AVERAGE BUBBLE INCIDENCE SCALE: 0 (NO BUBBLES) TO 5 (MOST NUMEROUS) (27)
	min.		
3–10 sec.	12	81	5 to 2
30 sec. to 1 min.	7	92	3 to 1
2 min. to 5 min.	13	66	2 to 0
6 min. to 8 min.	17	80	1 to 0
10 min.	30	15	0

Similar considerations appeared to control the death of animals receiving injections of air at varying rates into peripheral vessels (140).

Decompression from high pressures and to altitude. The principle that decompression from five atmospheres to one is far more hazardous than from one atmosphere to one-fifth of an atmosphere was demonstrated *in vitro* by Piccard (128). Water saturated with air gave brisk effervescence in the former case, and slow, delayed evolution in the latter. The total *volume* of gas available for release was the same in both instances. The explanation (68, 128) lies in the greater *weight* of gas dissolved at the high pressure, and consequently the greater number of gas molecules available for diffusion into gas nuclei (or for the formation of aggregates of gas by collision). This determines the rapidity of bubble formation, when the pressure is suddenly released. An *in vivo* counterpart of this demonstration is shown by a comparison of bubble frequency and distribution in guinea pigs decompressed from 105 lb/sq. in. gauge pressure to atmospheric pressure, and in rabbits decompressed from ground level to 45,000 feet (51). Bubble formation was far more severe in the former case (table 2) although the relative pressure reduction was seven to one in both. These results are entirely

similar to those reported by de Burgh Daly et al. (37, 43) who compared the results of decompressing rabbits, guinea pigs and rats from 6.3 to 1.0 atmosphere, and from 1.0 to 0.16 atmosphere. It is clear that the reduction in pressure by one half employed by Boycott, Damant and Haldane (21) would actually become more hazardous as the initial pressure increased.

Composition of gas bubbles. It was conclusively shown by Paul Bert (18) that nitrogen formed the major constituent of gas bubbles recovered from animals after decompression from compressed air atmospheres. The rôle played by CO_2 in bubble formation has given rise to some speculation as to the composition of gas bubbles at the site of formation. Gas diffusion constants for the common respiratory gases are approximately equal, and the composition of a bubble will

TABLE 2

Comparison of the distribution of gas bubbles in rabbits decompressed to a simulated altitude of 45,000 feet with guinea pigs decompressed from compressed air at 105 lb. per sq. in. (gauge)

	HIGH PRESSURE	LOW PRESSURE
Extravascular gas bubbles		
Adrenal	Numerous	None
Nerves	Numerous	None
Fat (intracellular)	Numerous	None
Blood vessels		
Arteries and veins	Present	Present
Capillaries	Present	Fat only
Spleen		
Sinusoids	Present	Present
Arteries and veins	Present	Present
Branches of pulmonary arteries	Present in many	Present in few
Liver		
Sinusoids	None	None
Central vein	Few	Few
Liver cells	Watery vacuoles present	No watery vacuoles present
Intestine	Numerous	Few
Muscle	Numerous	Few

therefore be largely controlled by the amount of gases close to it (38). Carbon dioxide is some 50 times more soluble in water than nitrogen. In CO_2 rich regions, such as a contracting muscle, this gas may condition the formation of the primary bubble and represent its principal constituent, at least for a while. Recent experiments (69, 110) support the rôle of CO_2 as a facilitator in bubble formation. When the bubble rich in CO_2 is moved to a body region rich in nitrogen and poor in CO_2, the latter gas will diffuse out and nitrogen in, to give bubbles essentially composed of nitrogen.

Gas Uptake and Elimination. Mathematical principles. Since the first demonstration of the importance of nitrogen in events leading to decompression sickness, attempts have been made to analyse experimentally and describe theoretically the course of gas uptake or elimination when the ambient pressure is raised or

lowered. That gas uptake would present the characteristics of a logarithmic relationship was recognized by Zuntz (185) and by Heller, Mager and von Schrötter (80). Employing the findings of Vernon (168) on the high solubility of nitrogen in fat, Boycott et al. (21) also presented a logarithmic relationship, but indicated a slower rate of saturation per round of circulation than the above authors. They stated further that their computations gave a rough approximation only to the actual rate of saturation for the body as a whole, due to variations in blood flow to the several tissues and to differences in body composition. Experimentally they found in goats a 94 per cent saturation in 3 hours. From this they deduced a similar degree of saturation for man in 5 hours. In computing decompression tables for divers, they arbitrarily assumed the existence of tissues having half saturation times of 5, 10, 20, 40 and 75 minutes, while admitting the possibility of tissues saturating at yet slower rates. Campbell and Hill (23) showed that about one third of the gaseous nitrogen of the human body was removed in the first few minutes while breathing 100 per cent oxygen, but some tissues were found to remain unsaturated after several hours' excess pressure (24). Hawkins, Shilling and Hansen (76) from a study of a large series of experimental dives modified the British decompression tables. They also adhered to the assumption of tissues having half saturation times of 5 to 75 minutes. Decompression times were radically reduced, especially for dives of short duration, in which the "slow" tissues would have become only partially saturated.

That saturation and desaturation curves should be reciprocal was indicated by Boycott et al. (21) and shown experimentally by Shaw et al. (146). The latter further showed that nitrogen absorption obeys Henry's law. A somewhat different concept was introduced by Behnke and his co-workers (5, 6, 7, 8, 12). Total nitrogen of the body was considered to be partitioned between aqueous and fatty phases, and the curve of nitrogen elimination was represented as the sum of two exponential expressions governing respectively the "water" nitrogen and the "fat" nitrogen. There was satisfactory agreement between nitrogen elimination found for man, and that calculated from the equation:

$$Y = \underset{\text{(water)}}{382\,(1 - e^{-0.0085\ t})} + \underset{\text{(fat)}}{458\,(1 - e^{-0.093\ t})}$$

where Y = total elimination of N_2, t = time in minutes, e = base of natural logarithms (12).

Some question was expressed subsequently of the adequacy of the k values cited above. Underwoood and Diaz (164) injected radon into the saphenous vein of the dog and studied its elimination through the lung at one minute intervals for four minutes. Part of the gas in the body was shunted to regions of poor circulation and was not measured in the short time interval allowed. They found k values of 0.66 as compared with the much smaller values obtained by Behnke (12), and believed that their figure applied to gas leaving the blood whereas the Behnke values were for gas entering the blood from tissues. This finding was held to resolve the difficulty encountered by Shaw et al. (146) which led to their postulation of a peculiar state of nitrogen supersaturation *in vivo*

Smith and Morales (150, 151), Morales and Smith (117, 118, 119), Jones et al. (90), and Ferris et al. (48) have contributed further to the analysis of blood-tissue gas exchanges and it becomes necessary to establish the general trend of such attempts to date. It appears to be implicit in the work of Boycott et al. (21) that the total body nitrogen reservoir may be represented as the sum of 5 (or more) arbitrary "tissues" with half saturation times of 5 to 75 minutes. Shaw et al. (146) and Behnke et al. (12) also considered that nitrogen elimination could be represented empirically by one or more exponential equation of the form

$$Y = A\ (1 - e^{-kt})$$

where Y = amount of N_2 eliminated in time t (minutes), A = amount of N_2 originally present, k = constant of elimination, e = base of natural logarithms.

In actual practice two such functions were used and referred to water and fat phases respectively. Underwood and Diaz (164) generalized from the work of these latter authors to the form

$$Q = \Sigma_i Q_0\ (1 - e^{-k_i t})$$

where Q = total amount of gas eliminated, t = time in minutes, ${}_iQ_0$ = initial amount of gas present in the i state (i.e., in water, fat, etc.), k_i = elimination constant for the i state, e = base of natural logarithms.

Smith and Morales (150) in developing an equation for the uptake of inert gas by tissue regions, e.g., the tissues of a limb, considered the following physical and physiological factors to be operative in gas exchange: blood volume of the region, delivery rate of blood flow, delivery concentration of gas in the blood, tissue volume, gas solubility in each tissue, area of the capillary bed, and tissue permeability to the gas. They derived an expression for tissue regions identical in form with that of Underwood and Diaz (164) but in which the various Q and k values were invested with physiological meaning. These quantities are not to be considered as characteristics of a specific tissue component (water or fat, etc.), but are functions of all tissues of the region, and of the circulation. They concluded (117) that the early, more rapid absorption stage is governed by the blood and by aqueous tissues in close relation to it, and the slower, later stages predominantly by fatty tissues; that these processes are nevertheless simultaneous and conditioned by physical and physiological factors whose importance varies from tissue to tissue and from region to region. These factors may be varied, e.g., by the substitution of one inert gas by another, by increasing blood flow to a region and by altering the degree of fatness. By the method of deriving the general equation employed by these authors, the effects of altering these variables are claimed to become predictable. Further, these quantities may be measured independently of gas uptake, and substitution into the equations developed gave agreements held to be close enough to justify the method of approach (117). Jones et al. (90, cited 117) found curves for nitrogen desaturation of the whole body to conform to the general equation. They emphasize in particular the rôle of the circulation, and believe that all their results are explainable on the basis of gas solubility and blood-tissue perfusion rates.

Gas solubilities. The greater susceptibility of fat individuals to decompression sickness was noted by Boycott and Damant (20) who deplored the fact that increase in experience and technical skill should so often be associated with the increasing waist that accompanies the onset of middle life. This susceptibility was attributed to the greater solubility of nitrogen in fat which becomes a gas reservoir maintaining nitrogen pressure long enough for bubbles to form during the pressure drop of decompression. From this time, considerations of gas solubility in body constituents have occupied an important rôle in the theory and practice of decompression sickness. It is generally held that tissues, with the exception of fat, take up gases in proportion to their water content (23). Data on the solubility of gases in plasma and body fat are incomplete, but their solubility in water and certain oils is better known. Since the effects of salts and proteins (74, 75, 144, 167) and the differences in the nature of the lipids (168)

TABLE 3

Solubilities, relative solubilities and ratio of solubility in oil to solubility in water of respiratory and inert gases presented in order of ascending molecular weight and density. Cited in part from ref. 161

GAS	MOL. WT.	DENSITY AIR = 1.0	SOLUBILITY IN WATER AT 37°C.	RELATIVE SOLUBILITY IN WATER He = 1.0	SOLUBILITY IN OIL AT 37°C.	RELATIVE SOLUBILITY IN OIL He = 1.0	RATIO OF SOLUBILITY IN OIL TO SOLUBILITY IN WATER
			cc/100 cc		*cc/100 cc*		
H_2	2.0	0.0695	1.6	1.9	4.5	3.0	2.8
He	4.0	0.138	0.85	1.0	1.5	1.0	1.7
N_2	28.0	0.963	1.3	1.5	6.7	4.5	5.2
O_2	32.0	1.105	2.4	2.8	12	8.0	5.0
A	39.9	1.38	2.6	3.1	14	9.5	5.4
CO_2	44.0	1.529	56.0	66.0	87.6	58.0	1.6
Kr	83.7	2.868	4.5	5.3	43	29	9.0
Xe	131.3	4.525	8.5	10.0	170	110	20.0
Rn	222	7.526	15	17.5	1900	1300	126.0

on gas solubility are relatively small, the values for water and oil may be used as first approximations for plasma and fat (12, 23, 168). Oil and water solubilities of H_2, O_2, CO_2, N_2 and of the inert gases He, Ne, A, Kr, Xe, Rn have been recently critically examined and tabulated (161). Values for some members of the series were newly derived using a radioactive isotope technique, while other values were derived from the older literature. Some of these results are included in table 3.

Nitrogen. If the fat content of the body is 15 to 20 per cent, the fivefold greater solubility of nitrogen in fat compared with water implies that one-half of the total nitrogen of the body is dissolved in fatty tissue (5, 12, 21, 23). During short exposures to excess pressure, fat may act as a reservoir to protect the body against sudden flooding with bubbles (5). Times for essentially complete saturation of the body by nitrogen are given as: man, 5–6 hours (20, 23); dog, 3–4 hours (146); goat, 3 hours (21). Small animals saturate and desaturate much

more rapidly (21) and require higher pressure differentials to elicit bubble formation.

Oxygen. In atmospheres of compressed air, the amount of dissolved oxygen in tissues represents an inconsiderable part of the dissolved gases. However, the oil-water ratio for oxygen approximates that for nitrogen, and exposure to 100 per cent oxygen under pressure followed by decompression leads to the appearance of gas bubbles (53, 81, 83). For reasons believed to involve tissue damage by oxygen under pressure, bubble formation was of less intensity on decompression from oxygen atmospheres (53). In decompressions to altitude from oxygen at atmospheric pressure the formation of bubbles is greatly reduced, and pretreatment with oxygen is commonly employed for protection under these circumstances (28, 49, 177, 179).

Helium. A low oil-water ratio and the low solubility in both plasma and fat has rendered this gas relatively ideal as a diluent for oxygen in diving (6, 13, 15). The total body content of He at saturation is only 40 per cent that of N_2 and relatively less is present in the "slow" tissues. Time for helium elimination is approximately 50 per cent that required by nitrogen. There is a cutaneous diffusion of helium of 50 cc. per hour which increases rapidly above 28°C with the concurrent sharp rise in peripheral blood flow (14).

Hydrogen. The solubility characteristics of hydrogen are less favorable than those of helium and no special advantage is gained by its use. It has been employed in experimental diving work (183).

Argon, Xenon, Krypton, Radion. The oil/water solubilities of these gases increase roughly in proportion to their atomic weights (91). The last three have found application chiefly as radioactive tracers. Use of argon as a diluent for oxygen in compression studies has served to confirm the view that the production of a highly saturated reservoir of inert gas favors bubble formation. Symptoms of increasing severity were produced by gas mixtures in the following order: oxygen, helium-oxygen, air, argon-oxygen (53), conforming to the oil/water solubilities of helium, nitrogen and argon respectively.

Chemical composition of the body. Arbitrary resolution of the body into lean body mass and fat in studying abnormal pressure effects was suggested by Behnke (6, 9) and a theoretical formulation was developed by Morales et al. (115). The lean body mass, consisting of bone and other tissues, together with essential lipids, maintains in the adult a relatively constant composition. Body density was used as an index of obesity by Behnke et al. (10). By comparing body specific gravity with direct estimations of total fat in the guinea pig, Rathbun and Pace (134) formulated a quantitative relationship between them. A similar relation between specific gravity and fat content was suggested by these authors for man. Computations of body composition from inert gas uptake have been made (6) and methods involving the differential uptake of two inert gases have been suggested as a means of measuring watery and fatty tissues (91, 116, 123) but apparently have not been elaborated experimentally.

Analysis of the effects of decompression on individual tissues requires a breakdown of their composition in terms of fatty and non-fatty components. Values have been derived from the literature for the composition of some tissues of

particular interest in decompression (table 4). The fat content of bone marrow is high (56, 85, 173). Since bone marrow may represent from 2.2 to 4.4 per cent of the body weight, bone marrow fat may comprise up to one-fifth of the total body fat. The adrenal gland is relatively rich in fat (7.5–14 per cent) and in decompression from high pressures a fall in specific gravity of this tissue has been correlated with the presence of extravascular bubbles, paralleling the situation existing in fat tissue proper (52). Brain (156), nerve, liver and muscle are relatively poor in fat; the skin, as a rule, is somewhat richer than these tissues (66).

Tissue blood flow. Inert gas uptake depends among other things on the rate of blood flow, and heavily perfused organs saturate and desaturate rapidly (150). It may be assumed that urine originating in Bowman's capsule would reflect the gas tension of the glomerular blood. Hill and Greenwood (81) early showed experimentally in man that the pressure of nitrogen in the urine became equal to

TABLE 4

Fat content of body tissues and organs

TISSUE OR ORGAN	ANIMAL	FAT CONTENT		REFERENCE
		Per cent wet weight	Per cent dry weight	
Brain	Man	5–8		156
Yellow bone marrow	Pig	87–90		24
	Ox, sheep, horse	90–96		24
	Goat	90–95		24
Red bone marrow	Rabbit	70–90		173
Adrenal gland	Guinea pig	7.5–14 (calculated)	30–54	52
Nerve-sciatic	Guinea pig	5.1 (calc.)	10–24	52
Liver	Guinea pig	1.4 (calc.)	4.9 (range: 0.5–11.8)	52
Muscle	Guinea pig	1.7 (calc.)	6.8 (range: 1.0–16.5)	52
Skin	Rat	6.6–12		66

that in the alveoli within 10 minutes after exposure to increased pressure and that the excess nitrogen rapidly disappeared when the pressure was lowered. Behnke and Yarbrough (15) found that the saturation time for urine in men breathing a He-O_2 mixture was between 30 and 60 minutes, and desaturation time occupied the same interval in the absence of bubble formation. In the latter case, desaturation was delayed. It would be expected that organs with perfusion rates of a comparable order, such as the thyroid and the liver would saturate and desaturate with equal rapidity.

Values for blood flow through tissues and organs have been derived from the literature (table 5). Classical methods of measuring blood flow were used in most instances. However, Jones et al. (90) have calculated blood-thyroid and blood-liver perfusion rates from the exchange of radio-iodine and radio-phosphorus, respectively. Tissues with poor blood supply include fat, bone marrow and resting muscle; active skeletal muscle, heart muscle and brain have a moderate

blood supply and the kidney and thyroid have the richest blood flow. Lying outside this general classification are organs like the spleen with an intermittent circulation and the liver with its dual circulation.

Local peculiarities of the circulation may modify figures based on the total perfusion rate. Gersh (56) contrasted the intermittency and probably reduced rate of flow in splenic sinusoids with the relatively continuous flow in those of the liver. Hepatic blood flow has been estimated to be from one-third to one-seventh of the portal blood flow of the liver (63, 152). In decompression, the slower and presumably more saturated portal blood becomes diluted with less saturated blood from the hepatic artery, thereby lowering the tension of gas available for bubble formation. Organs having blood trapped in sinusoids may on the other hand be exposed to sharp pressure differences between the entering arterial blood

TABLE 5

Blood flow in tissues and organs

TISSUE OR ORGAN	ANIMAL	BLOOD FLOW	REFERENCE
		ml/1000g/min.	
Thyroid	Man	4000	90
	Mouse	3240	90
Kidney	Man	3000	90
	Man, dog, rabbit	3400, 3300, 3200	148
Brain	Monkey	850 (range: 600–1000)	40
	Man	650 (range: 460–1040)	142
Heart	Dog	500–750	47
Muscle (dilated)	Dog	57–570	124
(dilated)	Dog	110–580	178
Muscle	Man	24 (range 5-rest to 50-exercised)	90
	Dog	69 (range 30–130)	61
Bone marrow	Goat	26	24
Fat	Man	12–15	90

and the trapped sinusoidal blood, sufficient to produce extravascular or intravascular bubbles. The rapid saturation of all structures of the kidney related to the glomerular apparatus may not extend to portions of the renal tissue having a different vascular pattern.

Capillary density and surface. While descriptive accounts of the capillary distribution in tissues abound, quantitative studies relating capillary surface (S) to unit tissue volume (V) are largely lacking. Values for total and open capillaries of fat tissue were derived (54) from histological studies on injected and frozen-dried preparations respectively. The ratio S/V (cm^{-1}) was computed for fat-rich and fat-poor adipose tissue and compared with estimates for muscular tissue based on data provided by Krogh (101) (table 6). Open capillaries represented from one-half (fat-rich) to one-quarter (fat-poor) of the total capillary area of fat; a similar general relationship exists in muscle (147). For other tissues,

estimates of S/V by indirect means are probably subject to considerable error. Values have been given (147) for the number of red blood corpuscles per cubic millimeter of tissue, which may be regarded as a rough measure of the number of open capillaries. Accepting the fairly reasonable value of 1000 cm^{-1} as a measure of S/V of the capillaries of mouse heart muscle, values for some other tissues have been computed (table 7). Fat-rich adipose tissues have available for gaseous exchange one quarter or less surface than the most poorly supplied muscle, and fat-poor tissues barely equal the poorest muscle. The relative in-

TABLE 6

Capillary surface of tissues in relation to total tissue volume (S/V)

TISSUE	ANIMAL	S/V (cm^{-1})		REFERENCE
		Total (open plus closed capillaries)	Open caps.	
Fat Fat-rich	Rat	51.9	23.5	54
Fat-poor	Rat	222.2	64.1	54
Muscle (a)	Rabbit	190–513		42
(b)	Rabbit	150–295		153
(c)	Dog	494		101
(d)	Guinea pig		186–507	174
(e)	Mouse		486–923	174
Cardiac muscle	Man	1184		175

TABLE 7

Relative values of S/V calculated from the number of red blood corpuscles per c.mm. of tissue as estimated by Sjöstrand (147)

TISSUE	ANIMAL	NO. CORPS./C. MM.	S/V (cm^{-1})
Heart muscle	Mouse	350	1000
Brain-cortex	Mouse	85	240
Cerebellum	Mouse	115	330
Liver	Mouse	280	800
Kidney-cortex	Mouse	300	850
-medulla	Mouse	500	1400
Duodenum	Mouse	160	460
Pancreas	Guinea pig	125	360

adequacy of the capillary bed of fatty tissue is therefore demonstrated quantitatively (54).

Cerebral cortex and cerebellum compare unfavorably with muscle in respect of the capillary bed available for gas transfer. Cobb and Talbot (34) and Cobb (33) concluded that even the most vascular parts of the brain were only one-fifth as vascular as skeletal muscle. Within the central nervous system itself Craigie (35), from measurements of the total length of capillaries in sections of the central nervous system of the cat found the poorest part of the grey matter to be one and one-half times as richly vascularized as the richest part of the white matter. The same was true in the monkey. In the cat Wolff (181) found the

following relative vascularities: parietal cortex, 100; lateral geniculate ganglion, 91; globus pallidus, 58; nerve, 47; and white matter, 43. Thus the white matter is something under one-half as richly vascularized as the grey. In addition, capillaries in the white matter are said to be larger than those of the grey (33) which would make S/V values for the white matter even more unfavorable.

Occupying a somewhat intermediate position in the S/V scale is skeletal muscle which possesses nervous and humoral mechanisms capable of rendering effective large portions of the total capillary surface when active, i.e., at those times when the conditions for gas bubble formation are apt to approach the critical. Highest in the scale are cardiac muscle, kidney and liver which appear to possess a large effective capillary surface for gaseous exchanges that is available at all times.

PATHOLOGIC CONSEQUENCES OF DECOMPRESSION SICKNESS. *Central Nervous System. Pressure.* Little can be added to the classical description by Heller, Mager, and von Schrötter (80) of the neurological aspects of the syndrome of decompression sickness. The substance of their detailed description follows: After a latent period, symptoms of varying degrees of severity may appear. These may be general in scope (syncope, dizziness, aphasia), may include large body masses (paraplegia and paralysis of both lower legs, of both arms, of one arm and one leg, or both legs and one arm with a persistent spastic paralysis, loss of urinary and intestinal sphincter control), may include sensory paresthesias and hypo- or analgesia separately, or associated with motor disturbances, or may be confined to small motor or sensory units (paralysis of the left lateral rectus muscle, a single orbicular muscle, or the hypoglossal muscles on one side, labyrinthine deafness, or atrophy of the left optic papilla). Neural damage due to aeroembolism thus varies greatly, is non-specific, and unpredictable: 1, it may be extensive, covering large regions, or confined to minute structures; 2, it may be largely motor with a sensory component, or the latter may be dissociated; 3, it may be confined to areas supplied by cranial nerves or somatic nerves.

The pathologic changes in the central nervous system following damage by aeroembolism have been studied extensively in man and other animals ever since 1870. Because of numerous precautions taken to reduce the incidence of decompression sickness and because of the success of treatment when such accidents occur, the most satisfactory pathologic studies date back about half a century. The most prominent feature is the occurrence of areas of softening in the spinal cord. Although they may extend over the greater part of the spinal cord (18), they are most commonly limited to the thoracic cord (19, 29). They are less frequent in the upper lumbar segments (80, 184) and are rather infrequent in the cervical region (21, 80, 166, 184). The areas of softening are usually small and are more circumscribed in the white than in the gray matter. The small necrotic areas may fuse, and result in an apparent general softening in large regions (80). Necrosis is more common in the white than in the gray columns (80), and in the former, is most frequent in the anterior columns (21). The ascending degeneration of nerve tracts anterior to the site of multiple lesions, and the descending degeneration posterior to the region have been described by numerous pathologists (19, 80, 143, 145).

Heller, Mager and von Schrötter have described the individual lesions most

completely. In the necrotic regions of the white matter, the nerve fibers swell, degenerate and are completely resorbed. The glial meshes are spread during the edema which takes place. Sclerotic areas appear, radiating into the surrounding, less damaged nerve fibers. The cavity enclosed contains cellular detritus and myelin droplets, and some phagocytic cells. The cavity then becomes more regularly outlined and the walls of the surrounding blood vessels become thicker. In the gray matter, the same processes take place, but in the surrounding regions, nerve cells in all stages of chromatolysis may occur. The necrotic cavity is not as sharply outlined in the gray as in the white matter.

While hemorrhage may occur, it is infrequent and is definitely less prominent than the regions of necrosis described above (18, 19, 80, 171, 184). It may, however, be of greater significance when it occurs in the brain (18, 29) or in the inner ear (80).

Gas bubbles have been described in pial vessels of the spinal cord, medulla and cerebrum in autopsied men, and in other animals (18, 21, 29, 80, 122, 184). As it is difficult to ascertain whether these bubbles were present where described at the time of death, the observations of Pudenz (132) and of Wagner (172) are of greater significance. The former observed in a monkey the appearance of gas bubbles first in pial arteries and then in veins in cinematographs of the cortex exposed to view by the use of a lucite calvarium. The latter made essentially the same observations in a series of cats whose pial vessels were viewed continuously before, during, and after decompression through a Forbes window. A gas bubble was observed also in the ophthalmic artery of a dog (29). Also more reliable than the earlier accounts are the preliminary observations of Gersh, who preserved the sites of gas bubbles by the freezing-drying method. Gas bubbles were found in the spinal cord of guinea pigs directly after massive aeroembolism *only* in the blood vessels; they were present also in intraneural blood vessels of the sciatic nerve. There was no evidence to support the assertion of Boycott et al. (21) that gas bubbles occur extravascularly in the central nervous system. Finally, minute gas bubbles confined entirely to the myelin sheath were present in peripheral nerves of guinea pigs decompressed from high pressure atmospheres of argon-oxygen, air, helium-oxygen, and oxygen (53).

The general pattern of neurologic symptoms, pathologic changes and the distribution of gas bubbles in the central nervous system following decompression was outlined by Bert (18). It was confirmed and extended by the magnificent work of Heller, Mager and v. Schrötter (80) which the authors have leaned on heavily, and by later workers. Gas bubbles form in the circulating blood after a short latent period following decompression. Most bubbles are filtered out by the lungs; some bubbles, however, pass through the lungs, either by means of small arterio-venous anastomoses which may be assumed to exist, or through the capillary "lakes" of Sjöstrand (147). These bubbles are small, about 25 μ in diameter. When they pass through the heart and reach the central nervous system, they occlude small arterioles of the same order of magnitude (21, 52, 132, 172). Since the circulation in the central nervous system is largely terminal in nature, the venous blood flow and blood pressure in the region is reduced, and

gas bubbles appear secondarily in the veins. Another consequence of the terminal nature of the circulation is that nerve cells and fibers in the affected region are suddenly deprived of their major source of nutrients and oxygen. They rapidly degenerate in small, focal regions corresponding to the arterioles occluded by gas bubbles. The necrotic regions may be separate, or may fuse secondarily with adjacent foci to form larger areas of softening. The extreme rapidity with which nerve cells are irreversibly injured following occlusion of the circulation has been conclusively demonstrated by numerous workers (58, 92, 93, 94, 176, 180). The unpredictability of the site and extent of the lesion, as well as the magnitude of the symptomatology, are thus related to the site of lodgement of the gas emboli, which may be isolated or adjacent to others, and to the numbers of blood vessels occluded. It cannot be stressed too strongly that there is a large element of chance as to whether a given number of gas bubbles causing neural damage will result in minor or severe symptoms, depending on the nerve cells and fibers affected. The circulation in the gray matter of the spinal cord is somewhat anastomotic, and this may account for the fact that necrotic foci occur less frequently in this portion of the spinal cord than in the white matter. Another circumstance which protects the gray matter is the fact that the capillary density, and presumably the blood flow, is greater than that in the white matter (35).

Hemorrhage is a relatively unimportant factor in neural damage of decompression sickness. Although v. Leyden believed that expanding extravascular gas bubbles induced hemorrhage by laceration of blood vessels (171), the same result may take place due to the occlusion and weakening of small blood vessels. It is also possible that vascular congestion somewhat remote from the gas bubble and the cessation of the blood flow may result in hemorrhage. This was actually observed directly in mesenteric vessels of animals injected with small gas emboli (30, 162).

The appearance of minute gas bubbles in the myelin sheath of peripheral nerves after decompression is attributable to the large volume of gas in solution in the lipid phase of the myelin sheaths. While the lipid content of the brain is only 5–8 per cent (156), certain parts may be expected to be richer in lipid. It is on this account that the earlier English investigators attributed the alleged occurrence of extravascular gas bubbles to the release of the excess lipid-soluble gas (21). Apart from the necessity for confirmation, the conclusions may be modified as a result of the later work by Campbell and Hill (23), who showed that the brain of pressurized animals contains far less gas than expected. This discrepancy in gas uptake may possibly be explained by further knowledge of blood flow and capillary density in the brain. Similar investigations may aid in interpreting several other problems without a satisfactory solution: the predominance of lesions of the spinal cord as compared with the brain, the marked predilection for injury of the thoracic cord, and the relative severity of damage to the motor systems as compared with the sensory.

Altitude. Symptoms of damage to the central nervous system following decompression to altitude are rather uncommon, and pathologic changes are even

rarer. There is no evidence that lasting changes occur in the cerebral cortex (45), in spite of the appearance of irregular EEG waves with a low frequency and high voltage during or after decompression to extreme heights (182). No residual EEG changes were detected in individuals decompressed to 35,000 feet even while they were suffering from the chokes or the bends. In subjects free from the effects of *generalized* shock, some temporary damage to the higher centers may occur, for there may be temporary syncope, scotoma, headache (45), amnesia, and auditory agnosia (106), motor aphasia, slight facial paralysis, a positive Babinski in one leg, agraphia, and a stuporous condition (22, 59, 136). Other temporary effects of decompression to altitude on the central nervous system are changes in muscle tone and in the strength of a variety of reflexes, and localized sensory losses. The incidence of *temporary* dysfunction of the central nervous system was given as 0.28 per cent, of a large series of exposures at 34,000 feet with oxygen (22). Temporary damage of the central nervous system may be even rarer than indicated, because of the difficulty of ruling out simulated effects caused basically by emotional disturbances. The only recorded instance of uncomplicated *permanent* damage to the central nervous system was reported by Smith (149) who observed paralysis in the hind limb of a dog soon after explosive decompression to 45,000 feet.

Briefly summarized, it appears that: 1. Neurologic signs of damage to the central nervous system following decompression to altitude are rare, when compared with the consequences of aeroembolism from deep diving. This relative infrequency of lesions in the central nervous system must be attributed to the relatively smaller amount of gas in solution in the body at altitude. 2. With the single exception noted above, neural damage is temporary. This may be attributed to the reduced volume of gas present in the body at altitude and to the differential between gas bubbles assumed to exist in relation to the affected regions and the high oxygen content of inspired gases. This procedure of reducing the effects of aeroembolism has been recommended for caisson workers ever since the time of Paul Bert, and is in common practice at the present time (11). 3. The neural symptoms are non-specific. As in the case of diving, this property may be attributed to the factor of chance of where a given gas-bubble freely circulating in the blood will finally lodge, occlude the local circulation and cause temporary dysfunction.

Further complicating the picture is the possibility that gas bubbles may lodge in intraneural blood vessels, and thus cause local neural (at least temporary) damage. Gas bubbles were observed in such sites in a study of acute, fatal aeroembolism in rabbits (51). An exhaustive search for gas bubbles in rabbits decompressed to altitude was made by Trowell (160). His failure to find these may be due to the inadequacy of the method of fixation employed.

Lung. Pressure. As a consequence of aeroembolism gas bubbles may occur in the pulmonary artery and its branches and in the chambers of the right side of the heart in sufficient numbers to cause death through occlusion of the circulation and asphyxia. In order to achieve asphyxia, it is necessary for enough blood vessels to be occluded to reduce the pulmonary arterial blood flow by 52–66 per

cent (64). In addition there may be pulmonary hemorrhage, edema, emphysema, and atelectasis (18, 21, 46, 80, 82). Except for minor details, the mechanisms of injury were developed by the early workers in the field. Gas bubbles arising in venous channels pass through the right auricle and ventricle to the pulmonary artery. The emboli occlude larger and smaller branches, but, contrary to earlier assertions by others, never reach the capillary bed; they are sometimes present in bronchiolar vessels (51, 56). The smallest vessels occluded were 40 μ in diameter. This corresponds with the direct observations of Chase (30) on the mesenteric vessels of living animals that gas bubbles introduced into the arterial circulation never penetrate beyond arterioles of a similar diameter. The occlusion of arterioles of similar dimensions was reported in other sites also by Curtillet (36) and by Tureen and Devine (162). The occluded blood vessels may be markedly stretched at the site of the gas bubble, as well as centrally. It should be noted in passing that the lung differs from all other organs in that gas bubbles in this structure represent emboli, with no significant contribution of local origin. While nearly all gas emboli are retained in the lung, it has been believed from the earliest writers (18) that some pass through the organ to be distributed as arterial emboli by routes which are largely hypothetical: 1, intrapulmonic arterio-venous anastomoses (36), and 2, the blood "lakes" described by Sjöstrand (147).

The relation of experimentally induced gas emboli in animals to aeroembolism appears to have been most extensively investigated by Heller, Mager and v. Schrötter (80). They found that the distribution of gas bubbles in both instances was strikingly similar. In the case of air introduced intravenously, the final distribution depended on the volume of gas injected, the rate of injection and the size of the gas bubbles.

Pulmonary hemorrhage, edema and emphysema have been shown to follow pulmonary embolization by solids (41, 165). Hemorrhage and emphysema have been attributed also to the violent rupture of alveolar walls (82). Pulmonary atelectasis as a result of decompression was first described by Bert, who attributed it to possible rupture of a vesicle at the time of decompression, thus permitting access of air under pressure to the pleural space. Other possible mechanisms are: 1, overinflation of the lung while inflating the Eustachian tube during compression; 2, expansion of air in alveoli and rupture of their walls, as a consequence of holding the breath (26); 3, escape of gas under pressure from alveoli to interstitial tissue, along the vascular sheaths to the hilus of the lung, pneumo-mediastinum, and pneumothorax (107, 108); and 4, rupture of a few alveoli into the retropleural connective tissue in the manner of a one-way valve, escape of this gas retropleurally to the hilus, pneumomediastinum, and pneumothorax (55). The mechanisms enumerated are applicable not only to the rare instances observed after decompression (4, 130, 131), but also to other equally rare situations: spontaneously (67, 120), in severe straining activity (111) and in cases of obstructed air passages, such as accompany diphtheritic laryngitis (39), following pertussis or other infections (31, 96, 111).

Altitude. Hoppe-Seyler in 1857 (84) attributed death to occlusion of pulmo-

nary capillaries by gas bubbles. The few other observations on this phenomenon were contradictory. They showed that rather few bubbles appeared in branches of the pulmonary artery, while only one bronchiolar vessel was found to be filled with gas in the series of six rabbits studied. The small number of pulmonary bubbles as compared with those in animals decompressed from pressure is explainable by the smaller quantity of gas in the body of animals decompressed to altitude. The same observation has been cited also as one of several reasons for the belief that animals decompressed to altitude tend to die of embolism of the central nervous system, rather than of pulmonary asphyxia, a condition opposite to that believed to obtain in animals decompressed from high pressure atmospheres (27, 56).

Pulmonary hemorrhage occurred irregularly in rabbits decompressed to altitude (27). Smith (149), and Berg, Baumberger, et al. (16), found that it follows more regularly after explosive decompression of experimental animals, especially, as the latter found, when decompression took place during inspiration or the last two-thirds of expiration. Only two instances of mediastinal emphysema have been reported in men after explosive decompression (112). Pneumothorax, retroperitoneal emphysema, and pulmonary atelectasis also occurred in rabbits, especially after slow decompressions. The administration of nembutal or of carbon-dioxide mixtures predisposed to pneumothorax, while preoxygenation or the administration of ammonium chloride, lactic acid, or sodium bicarbonate did not affect the incidence of atelectasis (28). The mechanism has not been investigated.

The observations on rabbits confirmed in part earlier reports by a group of British investigators who described the occurrence of atelectasis, vascular congestion, and pneumothorax in rabbits, rats, and guinea pigs decompressed to altitude (49, 50, 77, 78, 79, 159). They showed that these changes were related to the final altitude, and were unaffected by the degree of anoxia or by the CO_2 content of the blood. In unpublished experiments, the writers found that atelectasis was more common in young than in older animals.

Blood vessels. Ever since 1857 (Hoppe-Seyler (84)) it has been known that bubbles are more commonly (sometimes exclusively) present in the large veins following decompression from high pressure atmospheres, or to altitude. This was attributed by Bert to the fact that venous pressure is lower than that in arteries. Harvey et al. (72) added another factor, namely, the higher CO_2 tension of venous blood, facilitating the growth of gas bubbles. Arterial gas bubbles, when present, were attributed by Bert to passage of some gas bubbles through the lung into the left side of the heart and their distribution as emboli. Under extreme conditions, where the effect of blood pressure becomes overshadowed by other factors, one would expect gas bubbles to arise in arteries in the same manner as in veins. The distribution of gas bubbles is in fact similar to that which has been described repeatedly after the rapid intravenous injection of large volumes of air. Smaller volumes of air (or air injected at a slow rate) produce bubbles that are confined largely or almost entirely to the venous system. After decompression from high pressure atmospheres, gas is sometimes present

in the capillary bed of several tissues (52), but this seldom occurs, and then in fat tissue only, after decompression to altitude (51). The difference must be attributed to the vastly greater amount of gas in the tissues in the first condition.

Recently it has been noted by direct observations of living animals that an arteriolar and capillary constriction may occur at altitude. This has been observed to take place in man, rats and frogs (99, 104, 121), though not in cats (125). Reed and Blinks (138) found that vasoconstriction was not related to bubble formation. They also found that it could be abolished by nerve section and by exercise. It was correlated in man with the prolonged refilling time of the finger nail bed and of the arm vein (99), and with reduced skin temperature (157). This group found evidence that the latter phenomenon is related to susceptibility to bends.

Knisely (99) failed to see evidence of intravascular sludge in men exposed to altitude, although he did describe vasoconstriction. On the other hand Patek, who failed to note any change in the caliber of blood vessels in cats, observed sludging (125). This may have been due to the anoxic condition of the animals.

Sludging was observed directly in the pial vessels of living animals injected intravenously with air or decompressed from high pressure atmospheres. It occurred after vascular occlusion by gas bubbles, presumably as a consequence of reduced circulation and anoxia (170, 172). End (44) regarded agglutination of red blood corpuscles as the causative factor of decompression sickness, and gas bubbles as a secondary event. Swindle et al. (154) attributed disturbed function of decompression sickness to the occurrence of fragile, non-gaseous plasma flocculates. Jacobs and Stewart (88) investigated these possibilities by studying rat blood exposed to high pressure atmospheres and then decompressed. They found no clear evidence of any change in sedimentation rate, tendency to rouleaux formation or in the aggregates of rouleaux. They failed to observe true agglutination of red blood cells, but did describe a tendency for blood platelets to form aggregates about small gas bubbles and to appear free in this form later. Such platelet aggregates could conceivably lead to occlusion of small vessels in certain regions of the body. Gersh and his co-workers paid particular attention to the possible occurrence of all of these phenomena and failed to detect them in animals decompressed from high pressure atmospheres or to altitude. As the method employed (fixation by freezing and drying) could be confidently expected to preserve such flocculates and aggregates, the failure to find them returns the causation of decompression sickness to the conventional realm of gas bubbles.

Fat Tissue. Pressure. Experience in diving or caisson operations is that accidents occur more commonly in fat workers than in lean. Heller, Mager and v. Schrötter (80) reported that animals rich in fat in the subcutaneous tissues, mesentery and pericardium are more prone to show abnormalities than lean animals. This was tested for the first time by Boycott and Damant (20), when they found that the time of survival of rats and guinea pigs after decompression from a stated pressure was related to their total fat content. This was confirmed in another way by observing the highest pressure which guinea pigs could survive when decompressed rapidly, and relating it to their total fat content. For ex-

ample, fat guinea pigs (average fat content 31.9 per cent) survive decompression from a pressure of 45 lbs/sq. in., but die when brought up from 60 lbs/sq. in.; on the other hand, lean guinea pigs (average fat content 8.2 per cent) usually survive decompression from an atmosphere at 90 lbs/sq. in. but die when brought up from 105 lbs/sq. in. (52). Using another criterion (i.e., the time of appearance of the first gas bubble), the tendency for bubble formation in resting cats was also found to be related to the fat content of the animal when it was decompressed from moderately increased pressures. But in active animals, or at greater pressures, this relationship was masked by other factors (70).

Fat tissue containing numerous gas bubbles appears foamy, like whisked white of egg (82). The bubbles may be intravascular as well as extravascular (20). As a consequence, in surviving animals, large masses of necrotic fat may be present, especially below the kidneys. In late stages, the necrotic regions are surrounded by a zone of giant-cells, with some of the fat converted to calcium soap (21). In guinea pigs, minute gas bubbles may occur in the intracellular fat inclusions of fat cells. In somewhat more severely affected animals, macroscopic bubbles which are extravascular and extracellular may occur. Intravascular gas bubbles may be present in fat tissue in the absence of the aforementioned bubbles. Hemorrhage and vascular distention are associated frequently with the occurrence of extravascular gas, especially in fat animals (52). Thus, it may be assumed that, when purpuric subcutaneous spots appear in divers, gas bubbles have occluded some blood vessels and vascular congestion and hemorrhage have taken place.

The genesis of gas bubbles in fat tissue may be reconstructed in some such manner as follows: Fat cells dissolve excess amounts of gas, especially nitrogen, during pressurization. During and after decompression, many fat cells enlarge due to the appearance in the fat inclusions of minute intracellular bubbles. Meanwhile dissolved gas passes from the fat inclusions to the tissue fluid and the circulating blood. Depending on a number of factors, gas continues in solution or forms visible circulating bubbles. When these exceed the diameter of the blood vessels, they occlude the circulation. Meanwhile, in some regions, the cells increase in volume more markedly due to the increased number of intracellular gas bubbles. These distended cells then rupture and discharge their contents into an irregularly outlined intercellular (extravascular) bubble which contains cellular debris, fat, and gas under pressure. About this time, some blood vessels occluded by gas bubbles are distended with blood, and others may rupture.

This hypothetical reconstruction of the events leading to the formation of gas bubbles in fat tissue is supported by evidence along at least three lines that certain physical factors are involved. These are as follows: 1. The increased solubility of gases in fat as compared with tissue fluid (see p. 368). Biological evidence may be cited. The occurrence of gas bubbles in fat tissue and their number are directly related to its lipid content. Extravascular gas bubbles occur only in lipid rich structures (fat tissue, adrenal cortex, myelin sheaths of peripheral nerves) (52). Finally, gases which are especially soluble in lipid (such as argon),

are much more effective in producing gas bubbles in these structures, while gases which have a low $\frac{\text{fat}}{\text{water}}$ index of solubility are relatively ineffective (53). 2. The increased amount of gas in solution in fat is directly related to the number of gas bubbles formed in fat tissue. This was illustrated by the greater severity of the effects of decompression when animals are pressurized at higher pressures. It was also shown by a comparison of the effects of argon-oxygen, and nitrogen-oxygen mixtures. Although the relative solubilities in lipid and tissue fluid of argon and nitrogen are nearly identical, the amount of the former in solution is over twice as great. The number of gas bubbles appearing in fat tissue is far greater when argon is used than when nitrogen is used. In both examples, variations in the number of gas bubbles occur although the size of the gas bubbles remains the same. The size of the gas bubbles is probably referable to some tissue property such as elasticity. 3. The poor capillary density of fat tissue is an important factor predisposing to bubble formation, since excess gas cannot be removed rapidly enough to avoid high ΔP values in the tissue (see p. 362).

Altitude. In contrast with the serious consequences of excess body fat for divers, fat is not of great significance in bubble formation on decompression to altitude. Harvey et al. (70) and Catchpole and Gersh (27) failed to find any correlation between the fat content of animals decompressed to altitude and the time of first appearance of intravascular gas bubbles, the severity of the symptoms, or the time of survival.

Extravascular gas bubbles do not occur. Gas bubbles have been observed in veins draining fat depots but less commonly than in blood vessels draining muscles (70). They were found to be somewhat more numerous in fat tissue than in others by Gersh and Catchpole (51). Fat is the only tissue where gas bubbles were present in the capillary bed.

Muscle. Pressure. Little emphasis is placed in the literature on muscular lesions following decompression except as a consequence of neurological damage, or in the case of regional infarct (169). Only in recent years has muscle acquired great significance in theories on the origin of gas bubbles. Bert (18) found bubbles to be present only in intermuscular fascia, and Boycott et al. (21) were unable to see gas bubbles in skeletal muscle. Harvey et al. (70) found that in anesthetized cats bubbles do not appear in veins draining largely muscular regions, although they are present in vessels from fat depots. On the other hand, in stimulated animals, bubbles arise only from large muscle masses. Both the Princeton and the California groups agree that violent activity increases the number of bubbles (70, 177). In normal, decompressed guinea pigs, gas bubbles were present in muscle in arteries, capillaries, and veins of all dimensions, but they were fewer in number than in blood vessels of fat depots (52). Under the same conditions, an equally small number of blood vessels were occluded after decompression from a helium-oxygen mixture, a larger number were observed after argon, and none were observed after oxygen.

Muscle is regarded as an important site of bubble formation, the gas phase appearing in regions of mechanical tension, whether this is induced by passive

movement, stretching, injury or stimulation. This is attributed to the decreased P obtaining near tendon attachments due to the local stresses (68, 110). It should be stated that in guinea pigs, although blood vessels near the knee joint were not noted for their density of gas bubbles, those accompanying the *long* tendons near the ankle joint displayed gas bubbles prominently (56). Also important are the increased volumes of gas in solution as a result of compression. The increased gas content appears to overshadow the facilitating action of carbon dioxide.

Altitude. In anesthetized, decompressed animals, relatively few gas bubbles appear, and these seem to originate in fat depots. In stimulated limbs, however, the numerous bubbles appear to arise primarily from muscle (27, 28, 69, 110). By direct visualization, no bubbles were found in muscles of decompressed rats, although they were present at autopsy in the vena cava and other large veins (104). Arterioles were observed to be constricted. On the other hand, small numbers of bubbles were described in decompressed rabbits in blood vessels of larger-than-capillary dimensions. The factors responsible for bubble formation are primarily: 1, local production of CO_2 in regions of muscular activity, so that gas nuclei or minute bubbles in regions of high CO_2-tension tend to expand rapidly; 2, mechanical tension induced by passive movement, stretching, injury or electrical stimulation, which results in regions of low pressure in the neighborhood of insertions (70, 72, 110, 177, 179).

Bone Marrow, Bone, Periosteum, Joints. Bone marrow. The occurrence of gas bubbles in bone marrow has been described only in acute preparations of guinea pigs decompressed from compressed air (56). It was rather unexpected to find that in yellow marrow which was equivalent to lipid-rich fat, intravascular bubbles were exceedingly rare and extravascular bubbles were absent while the fat of the same animals was filled with numerous bubbles in both sites. Only under more severe conditions of pressurization did extravascular gas bubbles appear, together with a larger number in arteries, sinusoids, and veins. The extravascular gas bubbles were frequently larger than in fat, more irregular, and with a tendency to be concentrated near bony spicules. Sometimes, they seemed to dissect the endosteum from the marrow tissue. Arterial occlusion by gas is probably the result of embolism. Venous and sinusoidal gas bubbles probably arise locally in the bone marrow due to the slow circulation (24), the increased amount of nitrogen stored in the inclusions of the fat cells, and the low blood pressure in the blood channels. The extravascular distorting bubbles probably arise in a manner similar to that described for fat tissue. Both the large size of the extravascular bubbles and their irregular distribution may be due to the intermittent flow of blood through some sinusoids. This would result in a high uptake of excess gas in some regions and a large t locally, with bubble formation, and in other regions, low uptake of gas and no bubble formation. The tendency for more bubbles to occur in relation to bony spicules and to dissect the endosteum may be related to the finding that some crystals tend to favor the origin of gas bubbles from gas nuclei (126). It should be emphasized again that gas bubbles in bone marrow are relatively scarce, and then even so they

occur only in extreme conditions. This is probably due to the retarded rate of saturation of bone marrow with excess gas and the reduced circulation.

Bone and periosteum.. Pressure. Bone necrosis as a result of decompression sickness was first noted in 1888 (163). The literature on the subject has been thoroughly reviewed by Kahlstrom, Burton and Phemister (95). Additional information has been supplied by Phemister (127), Coley and Moore (32), and Rendich and Harrington (139). The most detailed microscopic study was made by Kahlstrom et al. They found that when necrotic bone was situated in the epiphysis and bordered on joints, there were varying degrees of collapse of the weight-bearing portions, and invasion of the necrotic regions with new bone or calcification. The overlying articular cartilaginous surfaces were replaced by fibro-cartilage, resulting in arthritis deformans. When the necrotic bone was located in the diaphysis, or in the epiphysis removed from articular surfaces, replacement by new bone or calcification also took place, but collapse and deformation did not occur. Since these observations were made several years after the original trauma, the mechanism could not be determined exactly. They postulated two general methods by which gas bubbles could cause bone atrophy: 1, gas bubbles form in bone marrow and interrupt the circulation of bone, and 2, gas emboli in numbers of smaller branches of the nutrient artery occlude the osseous circulation. Both mechanisms were demonstrated in work on decompressed guinea pigs. In some instances, gas-filled Haversian vessels were observed (56). It should be pointed out that bone changes in caisson workers and divers are relatively uncommon, probably for the same reasons that were given to account for the scarcity of gas bubbles in bone marrow. Gas bubbles are even scarcer in the periosteum, where, only rarely, gas distended small blood vessels were seen (56).

Altitude. Only one systematic effort has been made to detect bone damage in men decompressed to altitude. No radiographic evidence of such effects was found in a rather large number of subjects with 5–100 hours' exposure at 35,000 feet or higher. Follow-up x-rays several years later were recommended (135). The probability is that bone damage will be exceptional, for the same reasons that neural damage in aviators is scarcer than in divers (see p. 375). Another solitary report on the appearance of periosteum in living animals failed to disclose any evidence of bubbles in this site (125). However, the altitude at which the animals were studied, and the rate of decompression may have been unfavorable.

Joints and periarticular structures. Pressure. Experimental studies utilized morphological methods for the demonstration of gas bubbles or their effects, and x-rays to locate gas bubbles photographically. In guinea pigs decompressed from high pressure atmospheres, gas bubbles may be present in the joint fat. But even when they are absent, blood vessels in the region, especially those adjacent to the long tendons are frequently occluded and distended by gas bubbles (56). With x-rays, only the larger blood vessels which were completely filled with gas, were recognizable. Bubbles in fat or connective tissue were indistinguishable, or when they were very numerous, were recognizable almost always as a general x-ray shadow. In only one instance, in which shadows suggestive of

bubbles were found, only a minute fraction of all the bubbles were recognizable as such, because of the small size of the bubbles, poor resolution and overlay (57).

Altitude. The only morphological studies reported were on the joints of living animals. The failure to find gas bubbles in the periarticular tissues may have been due, however, to experimental conditions (125). Webb and co-workers (174) attempted to correlate gas in tissues of the knee with pain, and found that pain is unrelated to gas in the joint space or in the suprapatellar bursa. Better statistical relationships of pain were found with x-ray photographs correlating, in decreasing order of success, with 1, streaks in tissues posterior to the joint capsule; 2, gas bubbles immediately posterior to the joint space, and 3, gas bubbles in the infrapatellar space. The streaks appeared to be extravascular collections of gas in the intermuscular fascial planes of the posterior tissues of the leg. The gas seemed to be disposed as a collection of minute bubbles and to have no relation to the *larger* blood vessels or nerves of the region. Similar findings were reported by Thomas and Williams (155), who pointed out that "streaking" may occur in the absence of pain, and that there was no characteristic x-ray picture with which pain is correlated. Lund et al. (105, 106) came to the same conclusion in their study on the origin of pain in bends, and expressed the belief that the demonstration of gas by radiographic measures alone can be expected to help very little in supporting theories on the intimate origin of pain. A similar attitude was expressed by Gersh (57), who pointed out the difficulties in interpreting x-ray photographs of gas bubbles in terms of finer anatomical structures.

Adrenal Gland. Pressure. Gas bubbles have been detected in all layers of the adrenal cortex, as well as in the medulla. In addition, they have been observed in the capsular arteries, in the medullary veins and its tributaries, and occasionally in the reticular sinusoids. In all layers of the cortex, but most frequently in the fascicular zone, gas bubbles are present also extravascularly. Three major pathological consequences are 1, the occurrence of hemorrhages in the vicinity of the gas bubbles; 2, rupture of cortical cells in the region, and 3, vascular congestion in the sinusoids peripheral to the gas bubbles, with cessation or reduction of blood flow (52).

Two main factors are important in the origin of gas bubbles in the adrenal gland: the high content of lipid and certain peculiarities of the vascular pattern. The following sequence of events may be reconstructed: Gas bubbles begin as small occluding emboli in capsular arterioles and as clusters in the sinusoids of the reticular zone after the blood has passed through the fat- (and nitrogen) rich fascicular zone. These may grow and further occlude the circulation in the cortex. These areas of reduced cortical blood flow are small, and surrounding regions may have a normal circulation. With the two regions having different gas tensions, the gas bubbles continue to grow in the former region, and destroy the cortical organization, particularly in the fascicular zone, where the fat and dissolved gas is richest. The general disruption of structure is accompanied by hemorrhage, and also by a further sinusoidal congestion. Meanwhile, in the adjacent unaffected region, gas in solution is removed by the circulation either in solution or as minute bubbles which do not clog the sinusoids. Gas bubbles

arising in this manner may, in the capacious venous channels of the medulla, where the blood pressure may be smaller, expand to form large intravascular gas bubbles which may seriously interfere with the circulation throughout the gland.

Although gas bubbles appear in the adrenal gland of decompressed guinea pigs, it should be emphasized that they form somewhat less readily than in fat tissue. It is difficult to evaluate the clinical significance of the pathological findings. The temporary withdrawal of functioning cortical tissue may be related to the sense of exhaustion which divers frequently report after immersion.

Altitude. Gas bubbles were observed only in capsular arterioles and in some of the large venous medullary channels in rabbits; none were found in sinusoids or extravascularly (51).

Kidney. Pressure. Destruction of renal tubules of the cat was prominently figured by Boycott, Damant and Haldane (21). The proximal convoluted tubules of the cat are virtually unique because they are exceedingly rich in lipid, and it is unlikely that similar effects will occur in the kidney of other animals. In support of this assertion is the rapidity of the blood flow, and the brief desaturation time of renal tissue (see p. 370).

Altitude. Gas bubbles were present only in renal blood vessels of large caliber in rabbits decompressed rapidly (51).

Liver. Pressure. Boycott, Damant and Haldane (21) found numerous bubbles issuing as a froth from the cut surface of the liver of decompressed animals. These were believed to be confined to blood vessels. With methods less subject to artefact, very few microscopic gas bubbles were seen infrequently and only in central veins (52). Gas bubbles were common after decompression from a high pressure atmosphere of argon-oxygen (when some bubbles were observed in sinusoids), were rare after helium-oxygen mixtures, and were absent after oxygen (53).

A peculiar finding was the appearance of watery vacuoles in the cytoplasm of liver cells. The spherical vacuoles displace and distort the nucleus, and contain no fat stainable with Sudan III. They were present in liver cells not only after decompression from compressed air, but also from atmospheres of argon-oxygen, helium-oxygen, and oxygen. Their significance is unknown (52, 53).

The scarcity of bubbles in the liver may be explained by the work of Campbell and Hill (25) who found that liver has a rather slow half-saturation time. This may be due to the fact that most of the hepatic blood has already passed through a capillary bed and given up most of the excess gas. In addition to the reduction of the gas volume in the liver due to this factor, the nature of the arterial supply may contribute to the total picture during and after decompression. The less saturated arterial blood emptying into the sinusoids would tend to reduce the gas tension of blood in them and in the central vein and thus reduce the tendency for bubble formation.

Altitude. In decompressed rabbits, microscopic bubbles were observed very seldom, in the central vein and in the branches of the portal vein. The intracellular vacuoles observed in animals decompressed from high pressure atmospheres did not appear. They have, however, been described in men who died of the effects of exposure to altitude and in animals subjected to sudden reduction in

atmospheric pressure (103, 158). Ladewig gave good evidence to indicate that they may be related to low oxygen tension and anoxia rather than the effects of decompression. On the other hand, it is difficult to see how anoxia would play a rôle in the appearance of the vacuoles of guinea pigs decompressed rapidly enough from high pressure atmospheres to result in death in one to three minutes.

Spleen. Pressure. Gas bubbles occur in splenic sinusoids, arteries, and veins, in decreasing order of frequency, of guinea pigs decompressed rapidly from high air pressures (56). The sinusoidal bubbles are probably related to the intermittency of blood flow and possibly the reduced rate of blood flow in this structure. Both factors may result locally in regions of high gas tension (in closed sinusoids or in those with sluggish circulation) adjacent to regions of low gas tension (in narrow sinusoids with rapid circulation). If the volume of gas in the adjacent tissue is large enough, the gas bubbles grow and cause large, tearing defects to appear. The arterial bubbles are probably the result of gas emboli. The venous bubbles probably originate in situ because of the increased gas tension and decreased blood pressure.

Altitude. Fewer gas bubbles were present in the sinusoids of rabbits decompressed to altitude; they were present also in arteries and veins. In two rabbits, large, subcapsular, tearing bubbles were visible (51). The factors responsible for their appearance are probably the same as those described above.

Site of Origin of the Bends and the Chokes. Although much has been written on the subject, the literature dealing with unequivocal, direct evidence is distressingly scanty. If one makes the logical assumption that the pain of the bends and the chokes is due to gas bubbles, then from the point of view of the pathologist, those regions which are prone to bubble formation in man or other animals under less extreme conditions of decompression acquire the greatest significance as possible sites of the origin of pain. Whether pain results from distortion of nerve endings or nerve fibers by intra- or extravascular gas bubbles, or from local ischemia arising from reduced or occluded circulation is unknown. Gas bubbles have been described in muscle, intermuscular fascia, fat tissue, nerves, bone marrow, periosteum, and in fascial tissues adjacent to joints or to the long tendons. Except for fat tissue (where intracellular bubbles may occur in the cytoplasmic fat inclusion and also extravascularly) and for the myelin sheath of nerve fibers, no other extravascular gas bubbles have been noted in organs of locomotion. Even in these sites, gas bubbles may be seen in blood vessels in animals decompressed from high pressure atmospheres before they appear extravascularly; in animals decompressed to altitude, only intravascular bubbles occur. In all other regions, gas bubbles are confined entirely to the blood vessels. Thus, granting the primary assumption, the conclusion seems inescapable that the site of origin of gas bubbles is primarily vascular, though it cannot be denied that the extravascular gas bubbles may in addition cause pain by distortion. The evidence is cited in previous sections for the conclusion that the blood vessels most likely to be involved in the causation of the bends are those in the vicinity of the joints or tendons near their origin or insertion. However, others located in

nerves, muscles, or fasciae (including periosteum) may also be additional sites where pain may originate. A similar analysis of the anatomic basis of the pain of the chokes leads to the conclusion that the most likely sites of origin are the branches of the pulmonary arteries.

The conclusions derived above must be modified to a certain extent in the light of evidence showing that vascular occlusion by a gas bubble is accompanied by vascular congestion (30). If pain arises from vascular distention, then the same blood vessel or branches thereof somewhat removed from the gas bubble may be stretched to nearly the same extent. If pain arises from ischemia, then any point in the anoxic region may result in stimulation of the proper nerve endings or fibers.

Effects of Exercise and Drugs on Aeroembolism. Pressure. The conflicting claims of the effects of exercise on divers may be resolved by a critical analysis of studies by Harris et al. (68) and by Harvey et al. (70). The first group found that the minimal pressure which results in the liberation of bubbles after decompression is markedly lowered as a result of exercise. It may be assumed that as the pressure is increased greatly over this minimum value, the amount of gas present in the body outweighs in importance the decreased P which accompanies muscular activity. The result of this is that it would be difficult in practice to show that there is any relationship between exercise and amount of gas bubbles formed on decompression from higher pressures.

The effects of exercise were illustrated in another way by the use of anesthetics. Anesthetized animals, probably as a result of decreased muscular tone, had a much higher minimum effective pressure. Harvey and his colleagues (70) made similar observations, and found that a clear relationship between exercise and bubble formation existed on decompression from lower pressures, but that this is masked after higher pressures. From these results it is possible to understand that in divers, where the time under pressure, the pressure, and the rate of decompression are not often duplicated in experiments, some workers may claim that exercise is harmful, ineffective, or even beneficial in preventing or ameliorating the bends. Harris et al. (68) also reported that the use of anesthetics reduced bubble formation markedly, probably as a result of decreased muscular tone.

Oxygen administration is used effectively for the prevention and treatment of the more serious effects of aeroembolism in divers (5, 11, 89). This is confirmed by experiments on guinea pigs, in which far fewer gas bubbles in all sites were noted after decompression from oxygen as compared with nitrogen (53). This is difficult to understand, as the solubility properties of both gases are very nearly identical. Certain phases of decreased aeroembolism may be explained by assuming that oxygen of gas emboli is used metabolically, thus, in effect, reducing l at the site of bubble formation.

Altitude. The accelerating effects of exercise on bubble formation in animals at altitude have already been described. They correspond with the well-known increased severity of symptoms induced in men decompressed to altitude under controlled conditions. The increased tendency to bubble formation is attributed

to decreased P in the region of tendon attachments, and increased local t values due to excessive accumulation of CO_2.

Preoxygenation is effective in delaying the onset of symptoms of aeroembolism in men, and in protecting animals against bubble formation (see p. 369). This effect is achieved presumably by substituting a metabolizable gas (reducing t) for nitrogen, which is largely eliminated during the period of preoxygenation.

The administration of ammonium chloride and lactic acid was also found to reduce the tendency to bubble formation in decompressed rabbits (28). In man (2, 3, 113) ammonium chloride increases tolerance to anoxia and improves subjective symptoms. The underlying mechanism in the latter studies appear to be a shift in the blood pH towards the acid side and correction of the alkalosis caused by hyperventilation and loss of CO_2. To the extent to which CO_2 contributes to the initiation of bubble formation at altitude, a lowering of the arterial CO_2 tension would be expected to hinder bubble formation. The administration of moderate concentrations of CO_2 or of sodium bicarbonate did not have a noticeable effect on bubble formation (28, 110, 177). Accordingly, it was not surprising that in men exposed for two hours at a simulated altitude of 38,000 feet, the symptoms were of the same order whether the subject breathed pure oxygen or oxygen diluted by CO_2 (60).

There has been no uniform interpretation of the results of administering vasodilator drugs. Aminophyllin has been claimed to alleviate, or to reduce the severity of the bends (180); on the other hand, it had no effect on bubble formation in animals (138). A favorable effect of d-amphetamine in reducing the incidence of incapacitating bends has been both proposed (87) and denied (141).

SUMMARY

The evidence is overwhelming that gas bubbles are the primary pathogenetic agent in eliciting the pathologic effects of decompression sickness. Whether they occur after decompression from high pressure atmospheres or to altitude, gas bubbles are chiefly intravascular, and they are held to be responsible for nearly all important phases of the syndrome of decompression sickness. Extravascular gas bubbles occur also under certain severe instances of decompression from high pressure atmospheres, but they are restricted to certain lipid-rich structures. The pathological effects may be vastly greater after decompression from high pressure atmospheres than to altitude. These are described in detail for the various tissues and organs of the body. An attempt has been made to relate earlier and recent findings to each other, and to the causative factors. Basic to an understanding of the mechanisms involved in the syndrome is a consideration of the physical factors responsible for the uptake and elimination of excess gas in the body. The following physical factors were subjected to analysis: intrinsic factors such as blood pressure, blood flow, tissue permeability, tissue activity, the chemical composition of tissues and the solubility of gases in body components, and extrinsic factors such as the type, rate and extent of decompression applied.

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Studies on Dysbarism: III. A Smooth Muscle-acting Factor (SMAF) in Mouse Lungs and Its Increase in Decompression Sickness

CHRYSSANTHOS CHRYSSANTHOU, FRITZ TEICHNER, GILBERT GOLDSTEIN, JOHN KALBERER, JR., and WILLIAM ANTOPOL

Levy Laboratories, Beth Israel Medical Center, New York, N. Y. 10003, and Department of Pathology, Mount Sinai School of Medicine of the City University of New York, N. Y. 10029

CHRYSSANTHOU, C., F. TEICHNER, G. GOLDSTEIN, J. KALBERER, JR., and W. ANTOPOL. *Studies on dysbarism III. A smooth muscle-acting factor (SMAF) in mouse lungs and its increase in decompression sickness.* Aerospace Med. 41(1):43-48. 1970.

A smooth muscle-acting factor (SMAF) was derived from mouse lungs. The procedure for extraction and partial purification is described. SMAF was shown to: (1) elicit contraction of smooth muscle, (2) potentiate smooth muscle contractions produced by bradykinin, acetylcholine, 5-hydroxytryptamine and histamine and (3) increase vascular permeability. The activity of SMAF was significantly higher in lung tissue from animals subjected to compression-decompression than in lung tissue of equal weight from controls. SMAF is probably a polypeptide or a mixture of polypeptides. Physicochemical and pharmacological properties differentiate SMAF from other polypeptides with similar actions. The possible role and significance of SMAF in the pathogenesis of decompression sickness is discussed.

IT WAS PREVIOUSLY REPORTED that bradykinin and possibly other humoral smooth muscle stimulating substances may be implicated in the pathogenesis of decompression sickness.[1] This hypothesis was supported by the following observations: (1) Several of the histologic changes seen in decompression sickness are similar to those produced by bradykinin, (2) bradykinin intensifies the pathologic alterations and increases mortality in decompression sickness, (3) bradykinin antagonists and certain anti-inflammatory compounds ameliorate or prevent development of the disease as evidenced by the striking reduction in mortality and absence or decrease in severity of the pathologic changes.

Seeking more direct evidence, the possibility that smooth muscle stimulating or sensitizing substances are released or activated in decompression sickness was explored. The present communication concerns a smooth muscle-acting factor (SMAF), extracted from mouse lungs, the activity of which increases in decompression sickness.[2]

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MATERIAL AND METHODS

Production of Decompression Sickness: Hereditary obese hyperglycemic mice which are susceptible to decompression sickness[3] were employed. These animals, weighing 38-65 grams, were obtained from Jackson Memorial Laboratories, Bar Harbor, Maine. They were housed in metal cages in animal rooms with controlled temperature (71 ± 2°F) and relative humidity (50%) and were fed Purina Laboratory Chow and water *ad libitum*.

Decompression sickness was produced in these animals by a method previously described.[4]

Preparation of SMAF: In each experiment, lung extracts were prepared from two groups, one consisting of five mice subjected to compression-decompression, the other of five controls. A total of 14 experiments were performed. In the extraction procedure, precautions were taken to avoid or minimize the possibility of *in vitro* activation of smooth muscle stimulating substances, and to protect active substances against enzymatic degradation. As soon as the animals were sacrificed (in the experimental group the animals that did not succumb were sacrificed 20 minutes after decompression), the lungs were rapidly excised, pooled according to group, weighed, and immediately placed in 1N hydrochloric acid (300 mg of lung tissue/ml) in a boiling water bath for ten minutes. During this heating period, the lungs were minced and homogenized by means of a glass tissue grinder with teflon pestle or by sonication. Following heating, the homogenates were rapidly cooled

in an ice bath, soybean trypsin inhibitor (200 mcg/ml homogenate) was added, and the pH was raised to 7.6. After centrifugation to remove coarse particulate matter the supernatants were dialyzed against 30 volumes of deionized water for 24 hours. The dialysates were concentrated under reduced pressure in a boiling water bath, and seven volumes of absolute ethanol were added. The precipitate formed was removed by centrifugation and discarded. The supernatant was placed in a boiling water bath and evaporated to dryness under reduced pressure. The residue obtained was extracted with 90% ethanol; the extract was centrifuged and the supernatant mixed with four volumes of ethyl ether. The precipitate formed was desalted on Sephadex G-10 and then fractionated on Sephadex G-25. When the absorption at 270 nm was plotted against the Sephadex G-25 fraction number, the resulting curve showed two distinct peaks. The first peak was completely separated from the second by repeated passage through the column. The eluates constituting the first peak were collected, lyophilized and used for bioassays and other tests. This material will be referred to as SMAF, an acronym derived from "smooth muscle-acting factor."

Bioassays: The bioassays for detecting and estimating smooth muscle stimulating and/or sensitizing activities of SMAF were carried out on isolated guinea pig ileum and hen rectal cecum suspended in a 5 ml bath of continuously oxygenated (95% O_2 and 5% CO_2) Tyrode's solution at 34°C and on rat uterus and duodenum suspended in a 5 ml bath of continuously oxygenated De-Jalon's solution at 28°C and 34°C respectively. Contractions were recorded on a Grass polygraph. In order to detect and estimate smooth muscle stimulating activity, SMAF from animals subjected to compression-decompression and from controls were introduced into the bath alone and the responses elicited by corresponding doses (derived from equal amounts of wet lung tissue) were compared to each other and to those produced by known amounts of bradykinin. When smooth muscle sensitizing activity to bradykinin, 5-hydroxytryptamine, acetylcholine and histamine was to be assessed, SMAF was introduced into the bath and after 2-3 minutes, without washing, followed by the addition of one of the above agents. Whenever SMAF potentiated the effect of any of the smooth muscle stimulating substances, the potentiation test was repeated and "bracketed" by responses to the smooth muscle stimulating substance alone. In some bioassays SMAF was preceded by introduction into the bath of chymotrypsin in order to determine whether this agent sensitizes the muscle to SMAF. According to Edery's findings,[6,7] which were confirmed in our laboratories, chymotrypsin sensitizes guinea pig ileum to various kinins, but not to substance P, eledoisin, and angiotensin. All bioassays were repeated two or three times on the same muscle preparation and at least once on another muscle preparation.

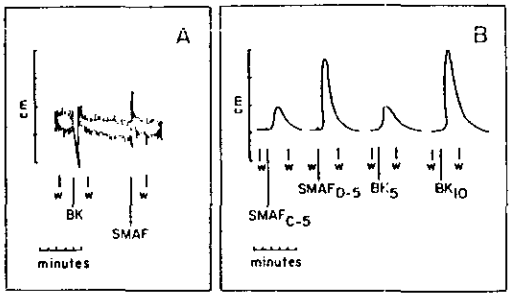

Fig. 1. A. Contrasting effects of SMAF and of bradykinin on rat duodenum. SMAF (5 mg wet lung tissue/ml bath), BK (bradykinin 20 ng/ml bath), w (washing). B. Comparison of smooth muscle stimulating activity of SMAF from controls and from decompressed animals on rat uterus. $SMAF_{C-5}$ (controls, 5 mg wet lung tissue/ml bath), $SMAF_{D-5}$ (decompressed 5 mg wet lung tissue/ml bath), BK_5 and BK_{10} (bradykinin 5 ng and 10 ng/ml bath), w (washing).

Permeability Studies: The effect of SMAF on vascular permeability was studied by utilizing the "blueing" of the rabbit's skin method. Pontamine blue (37 mg/kg) was injected intravenously in rabbits. Fifteen minutes later SMAF from decompressed and control animals was intradermally injected in the depilated abdominal skin at different sites. One hour after the intradermal injections the intensity and diameter of the resulting "blueing" was recorded. In some experiments, a mixture of SMAF and bradykinin or SMAF and histamine was injected in order to explore the possibility that SMAF may potentiate the effect of these agents on vascular permeability. The volume of each intradermal injection was 0.1 ml.

The following substances were used in these investigations: soybean trypsin inhibitor (5x cryst.) (Mann Res. Lab., Inc.), synthetic bradykinin (Sandoz), serotonin creatinine sulfate (Mann Res. Lab., Inc.), histamine dihydrochloride (Fisher Scientific Co.), acetylcholine bro-

TABLE I. COMPARISON* OF ACTIVITY OF SMAF FROM DECOMPRESSED ANIMALS AND CONTROLS

Effect on Smooth Muscle	Total No. Experiments**	Greater Activity In Decompressed (No. Experiments)	Greater Activity In Controls (No. Experiments)	Equal Activity (No. Experiments)	Statistical Significance
Stimulating	13	11	1	1	$P<0.001$
Sensitizing***	14	9	2	3	$P<0.05$

*SMAF preparations from decompressed animals and controls were compared in corresponding doses. (Derived from equal amounts of wet lung tissue).

**In each experiment two SMAF preparations were made. One from the pooled lung tissue of 5 animals subjected to compression-decompression, the other from the pooled lung tissue of 5 controls.

***Increase of the smooth muscle responsiveness to bradykinin.

mide (Matheson Coleman & Bell), crystalline chymotrypsin (Miles Chemical Co.), carboxypeptidase B-DFP (Worthington), pyribenzamine hydrochloride (Ciba), SQ 10, 643 (anti-serotonin compound, Squibb), atropine sulfate (Burroughs Wellcome & Co.), pontamine sky blue 6BX (DuPont).

RESULTS

Effects on Isolated Organs: Most SMAF preparations, both from controls and from animals subjected to compression-decompression, elicited slow responses of guinea pig ileum and rat uterus resembling those produced by bradykinin. SMAF also produced contractions of rat duodenum and hen rectal cecum in contrast to bradykinin, which caused relaxation or had no effect (Figure 1A). When SMAF from animals subjected to compression-decompression was compared to that from the control group in corresponding doses, the former produced an appreciably greater response in most of the experiments (Table I). Figure 1B shows that SMAF from control animals in a dose corresponding to 5 mg of wet lung tissue/ml of bath elicited a contraction of the rat uterus equal to that produced by 5 ng of bradykinin/ml of bath. A corresponding dose of SMAF from animals subjected to compression-decompression produced approximately a twofold greater response, corresponding to 10 ng bradykinin/ml of bath.

In addition to its smooth muscle stimulating activity, SMAF increased the sensitivity of smooth muscle to bradykinin, histamine, acetylcholine and 5-hydroxytryptamine. The potentiation of bradykinin was of greater magnitude and more constant than that of the other agents. Figure 2 shows that SMAF extracted from compressed-decompressed animals corresponding to 2.5 mg of wet lung tissue/ml of bath increased the response produced by 5 ng of bradykinin/ml of bath to that corresponding to 10 ng of bradykinin. In most experiments, SMAF from animals subjected to compression-decompression exhibited a greater potentiation of bradykinin than did corresponding doses of SMAF from control animals (Table I) (Figure 2). A dose response relationship was observed between the amount of SMAF and

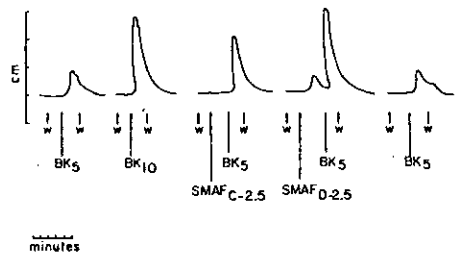

Fig. 2. Comparison of the bradykinin-potentiating activity of SMAF from controls and from decompressed animals on rat uterus. BK_5 and BK_{10} (bradykinin 5 ng and 10 ng/ml bath), $SMAF_{C-2.5}$ (controls 2.5 mg wet lung tissue/ml bath), $SMAF_{D-2.5}$ decompressed 2.5 mg wet lung tissue/ml bath), w (washing).

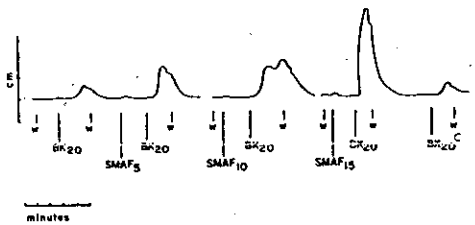

Fig. 3. Dose response relationship of the bradykinin-potentiating activity of SMAF on rat uterus. BK_{20} (bradykinin 20 ng/ml bath), $SMAF_5$, $SMAF_{10}$ and $SMAF_{15}$ (5 mg, 10 mg, and 15 mg wet lung tissue/ml bath), w (washing).

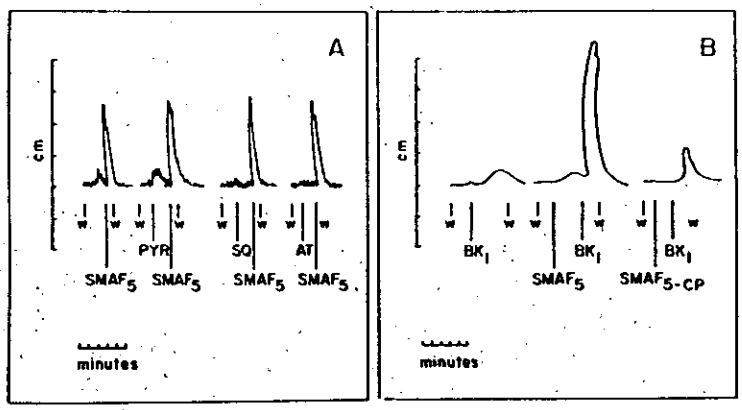

Fig. 4. A. Effect of antihistaminics, antiserotonin compound and atropine on the smooth muscle stimulating activity of SMAF on guinea pig ileum. $SMAF_5$ (5 mg wet lung tissue/ml bath), PYR (pyribenzamine 0.2 mcg/ml bath), SQ (SQ 10643 0.2 mcg/ml bath), AT (atropine 0.2 mcg/ml bath), w (washing). B. Effect of carboxypeptidase B on the smooth muscle stimulating and sensitizing activity of SMAF on rat uterus. BK_1 (bradykinin 1 ng/ml bath), $SMAF_5$ (5 mg wet lung tissue/ml bath), $SMAF_{5\text{-}CP}$ (Same as $SMAF_5$, but incubated with carboxypeptidase B), w (washing).

the degree of potentiation (Figure 3). SMAF in doses which, by themselves, did not elicit contraction increased the sensitivity of smooth muscle so that it responded even to subthreshold doses of bradykinin. The muscle stimulating activity as well as the potentiating effect of SMAF were not inhibited by antihistaminics, atropine, or antiserotonin compounds (Figure 4A), but were abolished or markedly decreased when SMAF was incubated with carboxypeptidase B (1 mcg/50 mg wet lung tissue) prior to its introduction into the organ bath (Figure 4B). The degree of SMAF inactivation by carboxypeptidase B was directly related to the incubation period.

When SMAF was tested following addition of chymotrypsin to the bath (0.2 mg/ml of bath), its smooth muscle stimulating activity was markedly potentiated. Chymotrypsin sensitized the rat uterus to SMAF to a greater degree than it did to bradykinin, since, following chymotrypsin, subthreshold doses of SMAF elicited responses greater than those produced by above threshold doses of bradykinin.

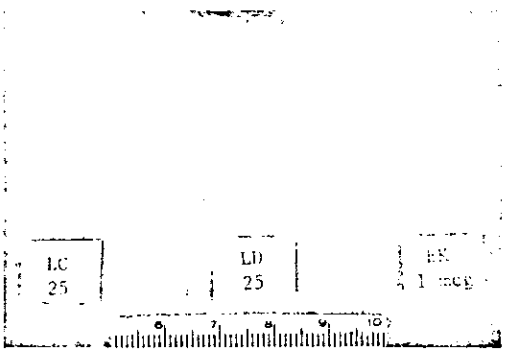

Fig. 5. Comparison of the effect of SMAF from controls and from decompressed animals on vascular permeability ("blueing" of rabbit's skin), LC (SMAF from controls, 25 mg wet lung tissue), LD (SMAF from decompressed animals, 25 mg wet lung tissue), BK (bradykinin 1 mcg).

Effects on Permeability: SMAF both from animals subjected to compression-decompression and from controls increased vascular permeability, as evidenced by the production of "blueing" in the rabbit's skin. SMAF from compressed-decompressed animals produced "blueing" over a larger area and of greater intensity than did corresponding doses of SMAF from control animals (Figure 5). The effect of bradykinin and histamine on vascular permeability was increased when these substances were mixed with SMAF. It was not possible, however, to determine whether this was a potentiating or an additive effect.

Physicochemical Properties: Considering the extraction and purification procedures of SMAF, it can be stated that the active agent(s) is heat stable (100°C), dialyzable, water soluble, ethanol soluble, and ethyl ether insoluble. The fact that it is dialyzable and can be inactivated by incubation with carboxypeptidase B suggests that the active factor(s) is a polypeptide or a mixture of polypeptides of relatively small molecular weight.

Differentiation from Other Similar Polypeptides: SMAF shares many of its physicochemical characteristics and biological effects with a number of known polypeptides, but it cannot be identified as any single one of them. Table II presents some of the differences between SMAF and some other biologically active poly-

TABLE II. DIFFERENCES BETWEEN SMAF AND SOME BIOLOGICALLY ACTIVE POLYPEPTIDES

	SMAF	Bradykinin	Subs. P	Angiotensin	Vasopressin	Oxytocin	Peptide B*	BPF**	Kutapressin***
Ethanol (Abs.) soluble	Yes	Slightly							
Inactivated by carboxypeptidase B	Yes		No				No		
Contraction of rat uterus	Yes							No	
Contraction of guinea pig ileum	Yes					Relaxation		No	
Contraction of rat duodenum	Yes	Relaxation			No	No			
Contraction of hen rectal cecum	Yes	Relaxation			Relaxation	Relaxation			
Inhibited by atropine (guinea pig ileum)	No			Partially					
Potentiated by chymotrypsin	Yes		No	No					
Potentiates bradykinin	Yes	No							
Potentiates 5-HT	Yes								No
Potentiates histamine	Yes							No	No
Potentiates acetylcholine	Yes							No	
Increases capillary permeability	Yes			Not in rabbits	No	No		High doses only	

*A bradykinin potentiating peptide released from fibrinogen by thrombin (see ref. 11)

**A bradykinin potentiating factor obtained from snake venom (see ref. 9)

***A bradykinin potentiating liver extract (see ref. 14)

peptides and agents which have been reported to potentiate bradykinin.[9,11,14]

DISCUSSION

The data presented indicate that SMAF prepared by the methods described is capable of eliciting smooth muscle contractions, of enhancing the responses of smooth muscle to bradykinin, 5-hydroxytryptamine, acetylcholine and histamine, and of increasing vascular permeability. The increase in the magnitude of contraction elicited by smooth muscle stimulating substances following addition of SMAF to the organ bath is interpreted as a potentiation of their action. This conclusion is based on the fact that the increase in the magnitude of contraction was in excess of that expected if it were due merely to an additive effect.

The exact chemical composition of SMAF has not been determined. Its dialyzability and its inactivation by proteolytic enzymes suggest a polypeptide nature. Further purification and characterization of SMAF is in progress. The possibility that the smooth muscle stimulating activity of SMAF is due to the presence of histamine, 5-hydroxytryptamine or acetylcholine can be ruled out on at least three counts: the method of SMAF preparation, its enzymatic inactivation by carboxypeptidase B, and the fact that antihistaminics, atropine, and antiserotonin compounds did not inhibit smooth muscle responses elicited by SMAF. The enzymatic inactivation of SMAF also excludes the possibility that its smooth muscle sensitizing activity might be due to thiol compounds (Glutathione, cysteine) which have been reported to potentiate the response of guinea pig ileum to bradykinin.[10]

SMAF resembles several smooth muscle stimulating polypeptides, particularly bradykinin, with which it shares many physicochemical characteristics and pharmacologic effects. In view of the above and considering the implication that SMAF is a new factor of polypeptide nature, its differentiation from similar biologically active polypeptides is necessary. Table II summarizes some of the differences between SMAF and other similar smooth muscle stimulating or sensitizing agents.

The fact that the activity of SMAF extracted from animals subjected to compression-decompression is greater than that of SMAF extracted from equal amounts of lung tissue from control animals suggests that SMAF may be released or activated in decompression sickness. This further supports the original hypothesis that smooth muscle stimulating substances are involved in decompression sickness.[4] The presence of SMAF in lung extracts of obese-hyperglycemic mice is not unique, since it was also found in thin mice[2] as well as in rabbits.[3]

The role of SMAF in the pathogenesis of decompression sickness may be due to its direct effects on smooth muscle and on vascular permeability as well as to its potentiation of the effects of humoral factors with smooth muscle stimulating activity. Direct effects on smooth muscle could cause bronchoconstriction and circulatory changes which may influence decompression sickness in a way similar to that postulated for bradykinin.[1] The increased vascular permeability produced by SMAF could cause extravasation of plasma and subsequently hypovolemic shock which has been observed as a complication of decompression sickness and has been considered a major factor in the death of animals after decompression.[5] The smooth muscle "sensitizing" effect of SMAF may have even greater importance. In view of the possible implication of smooth muscle stimulating substances in decompression sickness, agents which can modify tissue responsiveness to them may play critical roles. Minimal concentrations or even subthreshold levels of smooth muscle stimulants may produce significant tissue reactions when tissues are sensitized by SMAF. Certain investigators have considered the possibility of involvement of some smooth muscle stimulating substances in decompression sickness in rats but failed to demonstrate significant increase in their concentration in tissues following rapid decompression.[13] In the light of our findings, failure to show an increase in the level of these substances in decompression sickness does not necessarily rule out their involvement in the disease since they could elicit stronger reactions without an increase in their concentration if the responsiveness of the muscle is enhanced by sensitizing factors.

The mechanism by which SMAF is released or activated in decompression sickness is obscure. Activation of biologically active substances has been reported in shock[12,13] and following tissue injuries by mechanical pressure, burns, and freezing.[5] It is not impossible that among other triggering mechanisms, expanding gas bubbles, causing circulatory impairment, anoxia and mechanical injury of tissues may initiate reactions resulting in release or activation of SMAF. Speculations regarding the mechanism of SMAF activation or release, however, seem to be premature.

The possible significance of SMAF may extend beyond the pathogenesis of decompression sickness. SMAF or similar humoral agents may play important roles by modifying smooth muscle responsiveness to physiologic or abnormal stimuli.

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RECENT FINDINGS IN THE PATHOGENESIS OF DECOMPRESSION SICKNESS (DYSBARISM).

A.T.K. Cockett, R.M. Nakamura and J.J. Franks

A technique for the production of gaseous bubbles in dogs is presented. Plasma volumes decrease 4 to 38 percent of control values 4 1/2 to 5 1/2 hours after removal of 7 dogs from the decompression chamber. Red cell volumes do not change. The role of bubble formation with progressive reduction in blood pressure is discussed in the slower deaths of 10 animals. Bone marrow emboli were found on routine histologic sections of the lungs. (Authors' summary)

THIS PAPER IS PRESENTED IN ABSTRACT FORM ONLY BECAUSE THE CONTRACTOR COULD NOT AFFORD TO PAY THE REQUIRED FEE FOR PERMISSION TO PUBLISH.

Article abstract

Decompression sickness, which damaged the spinal cord, was produced in anesthetized dogs using a compression chamber. Cerebrospinal fluid pressure and several intravascular and intracardiac pressures were monitored during the course of the simulated dives. Manometric responses to forcible lung inflation and abdominal compression were measured both predive and postdive after signs of spinal cord damage were evident. Cinevenography of the epidural vertebral venous system was performed both predive and postdive. Histopathologic studies of the brains and cords of paretic animals were carried out. The results indicate that the epidural vertebral venous system becomes obstructed during spinal cord damaging decompression sickness and strongly suggests that spinal cord infarction in decompression sickness is caused by obstruction of cord venous drainage at the level of the epidural vertebral venous system.

Mechanisms underlying spinal cord damage in decompression sickness

J. M. HALLENBECK, M.D., A. A. BOVE, M.D., PH.D., and D. H. ELLIOTT, D.PHIL, M.B., B.S.

Decompression sickness is an illness of healthy young people that results from a reduction of environmental pressure sufficient to cause the formation of bubbles from gases dissolved in tissues. It may be considered as stemming from the local formation of bubbles in interstitial spaces, lymphatics, capillaries, and venules.[1-4] The population at risk includes an estimated 2 million sport (SCUBA) divers,[5] in addition to naval and commercial divers, high-altitude personnel exposed to hypobaric decompression, and compressed-air workers. Up to 34 percent of all cases of decompression sickness due to diving manifest some neurologic dysfunction,[6,7] and divers are in an age group where neurologic disability is especially likely to have a tragic socioeconomic impact.

The conventional view of decompression sickness would ascribe neuraxis damage to systemic arterial embolization of bubbles, with consequent capillary and precapillary obstruction.[3,4,8,9] For several reasons, the brain should be that portion of the central nervous system predominantly affected by systemic arterial emboli in decompression sickness. In clinical disorders associated with systemic embolization, such as subacute bacterial endocarditis, fat embolism, or the presence of a mural thrombus in the left atrium, the brain is a major target organ and the spinal cord is not.[10] Indeed, arterial embolization of the spinal cord is distinctly rare. In 3,737 autopsies from the National Hospital for Nervous Diseases in London, Blackwood[11] reported only 11 cases of vascular disease of the spinal cord, and in none was this due to arterial embolism. In fact, in current textbooks of neuropathology most authors, when describing arterial emboli, refer to the cord in addition to the brain only because the cord is the site of lesions in decompression sickness.

Further, it has been demonstrated experimentally by Van Allen, Hrdina, and Clark[12] that systemic bubble emboli distribute according to their buoyancy relative to blood. This accounts for brain involvement in arterial air embolism due to pulmonary barotrauma, and should, if arterial air embolism were the mechanism, also predispose to brain lesions in divers, who generally develop decompression sickness in an erect or sitting position. With the gross proportion of gray to white matter roughly the same in brain and cord, the brain constitutes

From the Bureau of Medicine and Surgery, Navy Department, Research Task M4306.01.1150AAK9, National Naval Medical Center, Bethesda.

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Dr. Hallenbeck's address is Naval Medical Research Institute, National Naval Medical Center, Bethesda, MD 20014.

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98 percent of the human central nervous system,[13] with 75 to 85 times more blood flow than spinal cord[14] and should receive proportionately more of any emboli distributing arterially.

Standing in stark contrast to the cerebral distribution of arterial emboli is the dominance of spinal cord involvement in the decompression sickness of subsaturation diving and tunnel work.[3,15,16] A review by one of the authors (A.A.B.) of 88 clinical reports of decompression sickness treated by the U.S. Navy over the past 20 years revealed that 77 percent of the central nervous system lesions were in the cord, while only 23 percent had any signs suggestive of brain involvement. Using the data of Kety[14] on distribution of blood flow to the central nervous system, the expected brain/cord ratio for decompression sickness lesions, if caused by arterial embolization, would be about 8, whereas in this survey it is actually 0.29. A chi-square analysis of these data indicates that a highly significant difference occurs ($p < 0.0005$) between the clinical observations and the expected pattern based on arterial flow distribution. This high incidence of spinal cord lesions is hard to reconcile with the above consideration if attributed solely to arterial bubble emboli.

Haymaker and Johnston[17] have postulated that bubbles formed in epidural and retroperitoneal fat enter the epidural vertebral venous system, causing congestion and flow retardation. Thus, they proposed that impaired spinal cord venous drainage due to epidural vertebral venous system congestion would facilitate bubble embolization of spinal precapillaries and arterioles to produce embolic lesions in the cord. We have explored the possibility that regions of the epidural vertebral venous system can become completely blocked and that this is associated with *venous* cord infarction.

Methods. Eight dogs anesthetized with morphine, 0.5 mg per kilogram, and chloralose, 100 mg per kilogram, were studied in the F.G. Hall Laboratory for Environmental Research at Duke University, Durham, North Carolina. A cuffed endotracheal tube was inserted and the balloon filled with water. Catheters were placed in the aorta, right ventricle, right atrium, azygos vein, and pulmonary artery. Electrocardiographic leads were connected to the extremities, and both respiration and intrathoracic pressure were monitored with a water-filled intra-esophageal catheter. A percutaneous cisternal puncture was performed in all animals for recording cerebrospinal fluid pressure. A doppler tipped catheter flow probe was placed in either the right ventricle or the root of the aorta to monitor bubbles large enough for detection. Needles were placed in the posterior spinous processes at several vertebral levels in four dogs for intra-osseous venography, and a catheter was placed in the common iliac vein in four other dogs for injection of contrast materials. A polyethylene catheter was inserted into the confluence of sinuses through a small drill hole in each of the four animals with common iliac vein catheters in order to inject contrast medium and measure pressures.

After the animal was prepared, the Statham® strain gauges were balanced and calibrated and control pressures were recorded. The manometric responses to lung inflation also were measured in six dogs. In these animals, changes in central venous pressure (CVP) and cisternal pressure (CSFP) could be compared. The manometric response was defined as the ratio between the rise in cisternal pressure and the rise in central venous pressure (ΔCSFP/ΔCVP) caused by forcible inflation of the lungs. This ratio may be expressed as the percentage of the rise of central venous pressure that is transmitted to the cerebrospinal fluid.

The normal mechanism in lung inflation involves an increase in CVP that is transmitted retrograde through patent azygos and patent intervertebral veins to the thoracic epidural vertebral venous system, where engorgement and distension induce a rise in CSFP. In abdominal compression, the rise of inferior vena cava pressure is transmitted to the cerebrospinal fluid in a similar manner, provided that intervertebral veins and the lumbosacral epidural vertebral venous system are patent. Therefore, in the absence of a subarachnoid block, a decrease in the manometric response suggests an obstruction of the epidural vertebral venous system or veins that drain this system.[18–22] A theoretical possibility that may explain a finding presented below is that an obstruction of the epidural vertebral venous system located at the periphery of a region of induced engorgement might actually augment a manometric response.

Control cinevenography was performed by various routes using Renograffin 76®, a water-soluble contrast medium. In three dogs, injections were made retrograde into the azygos vein using a constant pressure injector and, in addition, intra-osseous venography was performed at various levels. These techniques permitted visualization of the epidural vertebral venous system. In four other dogs, the epidural vertebral venous system was opacified by injecting Renograffin 76® into the common iliac vein while the inferior vena cava was collapsed by abdominal compression, and also by injecting contrast material into the confluence of sinuses during external jugular vein compression. Canine external jugular veins provide the major routes of cerebral venous drainage, and hence their compression is equivalent to a Queckenstedt maneuver in man.

After control pressures were recorded and control manometrics and cinevenography were performed, the animals were compressed, with air as the breathing medium, in the hyperbaric chamber at Duke University to simulate a dive to 220 ft at a descent rate of 75 ft per minute. The duration between the time they left the surface and the time they left maximum depth was 50 or 60 minutes, sufficient to produce decompression sickness in the majority of exposed dogs. Several dogs, however, required a second exposure at 220 ft for 15 to 20 minutes to produce signs of spinal cord dysfunction.

The rate of decompression simulated a 60 ft per minute ascent in seawater, and a stop at 40 ft was interposed so that the investigators could enter the pressure chamber from an adjacent lock, examine the dog, recalibrate and

zero the pressure gauges, and prepare for cinevenographic studies to be performed as soon as the dog showed signs of decompression sickness. These maneuvers at 40 ft usually took about 5 minutes, and the subsequent ascent to the surface, during which the dog was observed for indications of incipient decompression sickness, was made at the rate of only 5 ft per minute.

Continuous monitoring of the pressure data throughout the dive was possible because the gauges were vented to give pressure values relative to ambient pressure and the compression chamber was equipped with special connectors to carry the pressure signals through the chamber wall to a Gilson® polygraph outside.

When signs of decompression sickness, such as labored tachypnea ("chokes"), a rise in pulmonary artery pressure, a rise in central venous pressure, or a rise in cisternal pressure appeared, manometrics and cinevenography were repeated. These studies also were carried out when signs of spinal cord damage supervened. Signs of spinal cord damage included loss of tendon reflexes, loss of the segmental panniculus reflex below the level of the lesion (elicited by pinching the animal's flank with a hemostat), extensor rigidity of the extremities, and occasionally, paralysis of the intercostal muscles and diaphragm, requiring respiratory assistance.

In several supplementary studies, other conditioned male mongrel dogs were used at the Naval Medical Research Institute, Bethesda, Maryland.

In five animals, simulated dives, similar to those at Duke University, produced spinal cord lesions. Cisternal pressure responses, either to lung inflation through a cuffed endotracheal tube or to abdominal compression, were measured using an open manometer.

One dog was anesthetized, placed in a prone position, and subjected to systemic arterial bubble embolism from a catheter placed in the aorta at the level of the eleventh thoracic vertebra. Small increments of air were injected until a total of 100 cc had been delivered. Signs of spinal cord damage appeared and percutaneous cisternal puncture was performed, followed by manometrics. Cord damage was verified pathologically.

In two other animals given similar dive profiles at Bethesda, cisternal pressure responses to abdominal compression and lung inflation were measured, and when the responses were found to be blocked, 10 cc of air were gently introduced through the cisternal needle with the animal in a head-down, tail-up position. A standard x-ray was taken of the caudal spinal canal to detect any air in the caudal sac.

In pathologic studies done at the Naval Medical Research Institute, 25 dogs in which spinal cord lesions had developed after decompression and four dogs exposed to dives in which there were no abnormal neurologic signs were given a slow injection of 2.0 percent Evans blue dye, 5 ml per kilogram. Some 30 to 60 minutes later a catheter was placed at the root of the aorta via a retrograde femoral approach and 500 to 1,000 ml of saline were infused while blood was simultaneously allowed to drain from a severed external jugular vein. After the saline infusion, the animal was perfused with 500 to 1,000 ml of 10 percent formalin, and the brain and cord were later removed.

One other animal was anesthetized with 25 mg per kilogram of nembutal and given a dive of 220 ft for 53 minutes in the supine position to minimize the likelihood that buoyant bubbles would embolize arterially to the spinal cord. Following fatal decompression sickness, the brain and cord were removed for pathologic examination.

Results. The doppler findings and vascular pressure changes, which have been reported in detail elsewhere,[23] are summarized here in order to provide a comprehensive account of the sequence of events. Shortly after the doppler signal began to indicate incoming bubbles (figure 1), pulmonary artery systolic and diastolic pressures began to rise, reaching a mean postdive value of 54/32 mm Hg. This was followed in minutes by two changes in central venous pressure, a mean rise of 6.25 mm Hg and an increased fluctuation with respiration. Concurrent with the changes in CVP, there was a progressive and disproportionately large increase in CSFP, reaching an average level of 524 mm water. The signs of spinal cord damage appeared with or shortly after the rise in CSFP. The CSFP changes are summarized in the table. Maximum CSFP was reached an average of 7 minutes after the dogs surfaced from dives that led to signs of spinal cord damage. The range was from 1 ½ to 15 minutes. CSFP remained elevated for an average of 21 minutes, with a range of 14 ½ to 24 ½ minutes. In two animals the initial dive led only to "chokes" without signs of spinal cord damage; in one the CSFP did not change, and in the other a 27 mm water CSFP rise occurred but returned to predive level in 2 minutes.

Manometric responses to forcible lung inflation were measured in six of the dogs studied at Duke University. In five of these, predive manometric responses averaged 63 percent transmission, a value considered to be within the normal range.[24] After the signs of spinal cord damage had appeared postdive in these five dogs, the average transmission fell to 26 percent. The difference in these responses was significant at $p < 0.01$ by paired t-test. The sixth had a predive transmission that was somewhat high at 72 percent; after signs of cord dysfunction had appeared, the transmission rose to 100 percent. While we cannot definitely explain this paradox, we would suggest that the epidural vertebral venous system or the intervertebral veins were obstructed at sites that actually enhanced distension of segments of the epidural vertebral venous

Cerebrospinal fluid pressure (CSFP) changes during decompression sickness in eight dogs studied at Duke University

CSFP	Predive control	Post spinal cord involvement
Average	80 mm water	524 mm water*
Range	41-163 mm water	211-816 mm water

*Difference is significant at $p < 0.0025$ by paired t-test.

system during the lung inflation maneuver, such as at the periphery of the region of engorgement. Cinevenographic studies of the epidural vertebral venous system during the postdive period contrasted with predive films in three major ways. They showed congestion with stagnation, areas of obstruction, and the presence of moving or static filling defects in the epidural vertebral venous system, interpreted as bubbles.

Congestion with stagnation manifested as distension of the epidural vertebral venous system with increased radiodensity of the intravenous contrast material and retrograde opacification of posterior interspinous veins not visualized during the control injections (figures 2 and 3). Obstruction was suggested by retrograde azygos venography when contrast material injected from a single site and at constant pressure opacified the epidural vertebral venous system during the control period but opacified little or none of that system following signs of cord damage induced by decompression sickness. Intra-osseous venography suggested obstruction when the characteristic predive longitudinal opacification of three to six segments of the epidural vertebral venous system

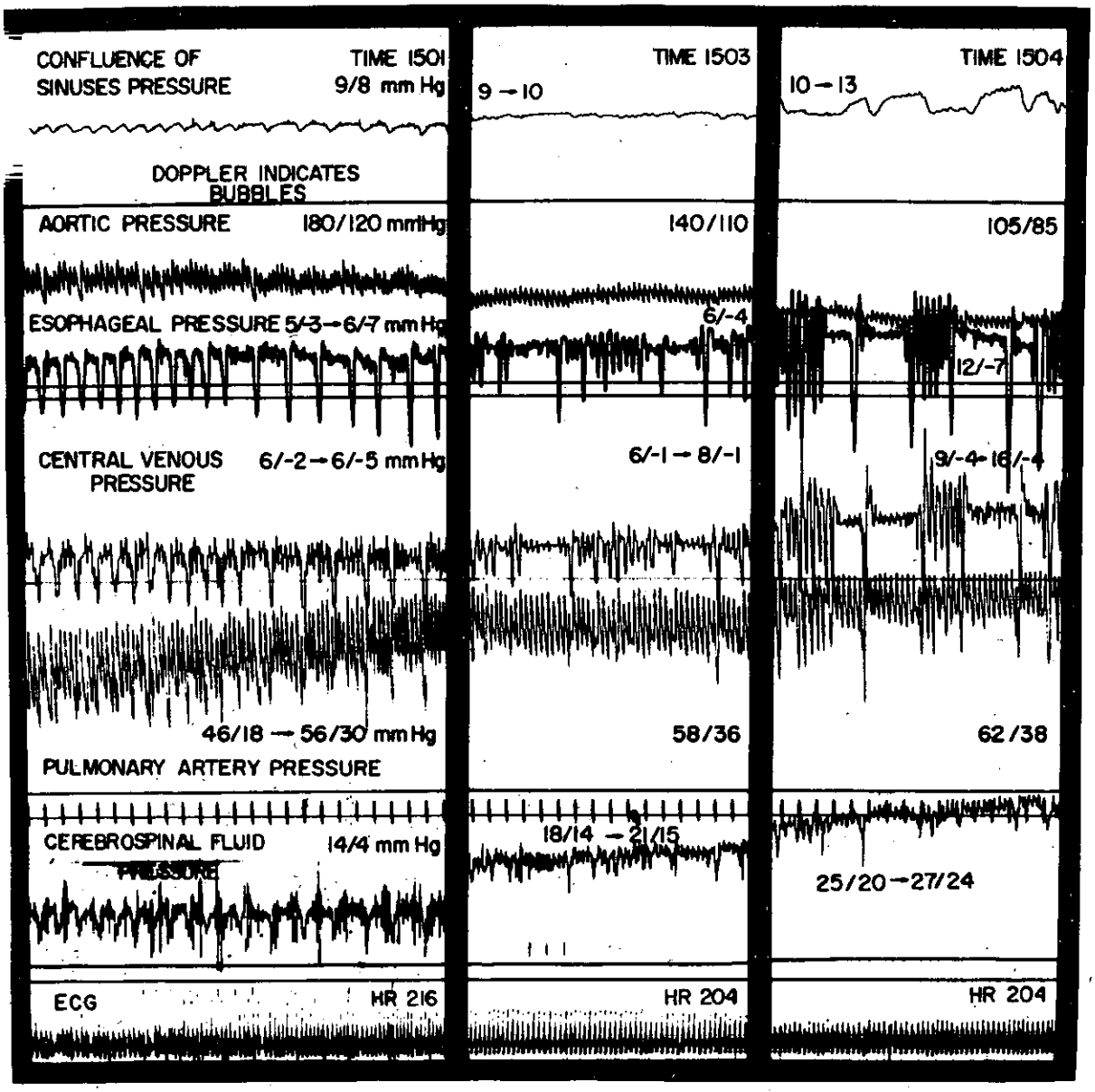

Figure 1. Juxtaposed segments from a Gilson® polygraph record of one dog showing representative sequential changes in various physiologic pressures.

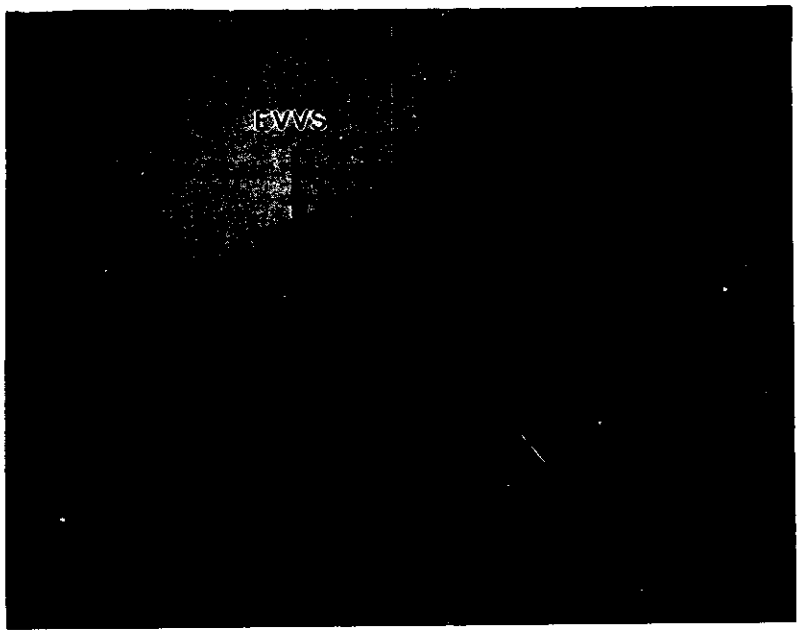

Figure 2. Cinevenographic still of a dog's cervical region predive. Contrast material was injected into the confluence of sinuses during external jugular vein compression. EVVS = epidural vertebral venous system.

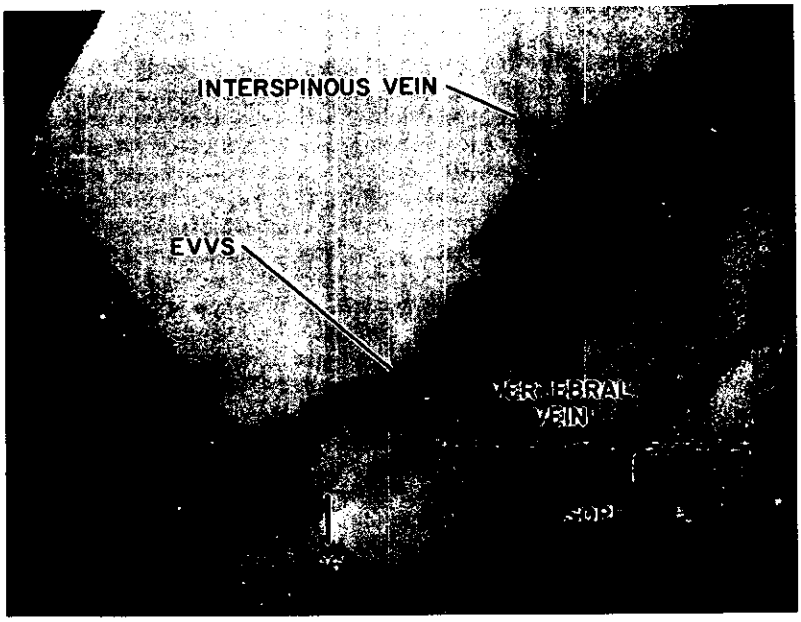

Figure 3. Cinevenographic still of a dog's cervical region during decompression sickness. Contrast material was injected into the confluence of sinuses during external jugular vein compression. EVVS = epidural vertebral venous system.

gave way postdive to egress of all contrast material through the intervertebral vein, draining the posterior spinous process injected.

The clearest evidence of obstruction was provided by common iliac vein injection, combined with abdominal compression, and confluence of sinuses injection, combined with external jugular vein compression. By using these techniques together, longitudinal filling of most of the epidural vertebral venous system was achieved in the predive period, and postdive, obstruction was signified by abrupt cut-off of the column of contrast material (figure 4).

Five of the seven dogs studied cinevenographically showed evidence of obstruction. Usually this was in the upper lumbar or the thoracic region. Of the two dogs that did not evidence obstruction, one showed severe congestion of the cervical epidural vertebral venous system, while the abdominal epidural vertebral venous system was not visualized because of technical difficulties. The other dog's epidural vertebral venous system was well-studied, and only widespread severe congestion was apparent. Congestion was evident in five of seven dogs studied. The most suitable technique for demonstrating congestion was by injecting via the

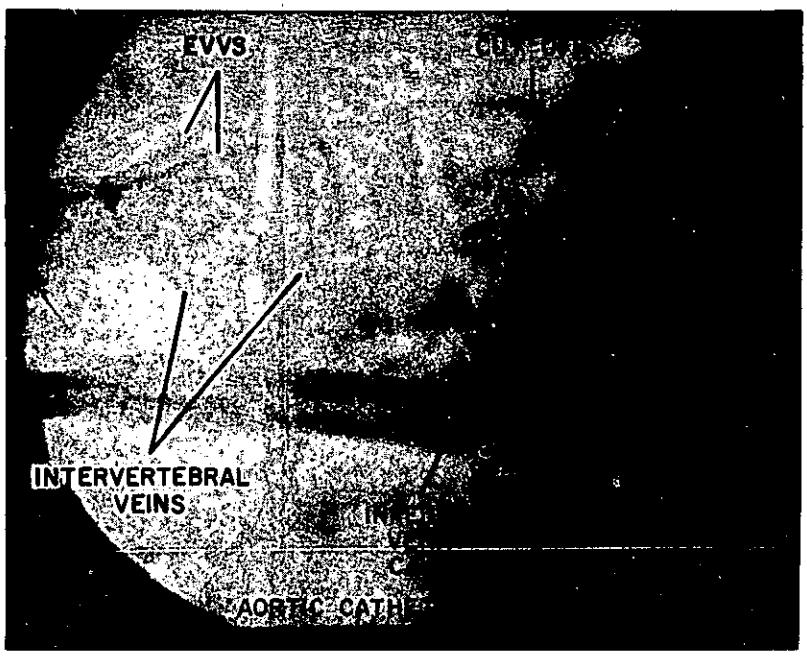

Figure 4. Cinevenographic still of a dog's upper lumbar region during paralytic decompression sickness. Contrast material was injected into a common iliac vein during abdominal compression. EVVS = epidural vertebral venous system.

common iliac vein and confluence of sinus routes. Using this approach, congestion was noted in four of four dogs. Bubble filling defects were seen in three of the seven animals.

A reduction of manometric response to lung inflation again was noted in five dogs with decompression-induced cord damage studied at the Naval Medical Research Institute. The cisternal pressure rise during lung inflation averaged 15 mm water in these animals, compared with a normal rise of 50 to 60 mm water. Abdominal compression also was performed in these five dogs, and in three, the rise in cisternal pressure was only 10 to 15 mm water. However, in the other two, the cisternal pressure rapidly rose 50 to 60 mm and then fell rapidly again, the normal response to abdominal compression. Intact abdominal manometrics with an attenuated response to lung inflation indicates that the transmission of intrathoracic pressure rise to the cisternal needle is obstructed. The site of this obstruction would have to be the epidural vertebral venous system, or veins connecting this system with intrathoracic veins, because any subarachnoid obstruction eliminating the lung inflation response also would eliminate the abdominal response.

In several animals, intercostal and diaphragmatic paralysis, accompanied by oral respiratory movement and unchanged heart rate and blood pressure, followed lung inflation or abdominal compression. It is as though maneuvers that congest the epidural vertebral venous system during severe decompression sickness can critically impede cord venous drainage in the cervical region, causing cervical cord damage and dysfunction.

One other dog was placed in a prone position and exposed to arterial air embolism from an aortic catheter placed at T-11. The purpose of this experiment was to investigate whether bubbles injected from a site that would facilitate cord embolization and consequent cord damage would lead to manometric changes. After signs of spinal cord damage had supervened, the cisternal pressure responses to lung inflation and abdominal compression were found to be normal. Histopathologic study of the animal's brain and cord revealed small perivascular hemorrhages in the gray matter of the cord, thus presenting a contrast with the usual white matter lesions that are characteristic of spinal cord damage in decompression sickness.

In two other animals with cord damage due to decompression sickness, manometrics measured with an open manometer were found to be blocked, and 10 cc of air were introduced through the cisternal needle with the dog in a head-down, tail-up position. A plain x-ray of the caudal sac revealed the presence of air and indicated that no subarachnoid block was present.

Twenty-nine dogs were studied pathologically at the Naval Medical Research Institute. The brains and cords of the four animals subjected to nonparalyzing dives were normal, both grossly and microscopically. Of the 25 dogs exposed to dives that produced signs of neurologic damage, the brain stem was involved in two and the spinal cord was involved in all. Neither cerebral nor cerebellar involvement occurred. In 20 of the 25 paralytic dogs, the lesions were grossly hemorrhagic and predominantly located in the white matter, with gray matter sparing (figure 5). This pathologic picture is not typical of arterial cord infarction, but is instead typical of acute venous cord infarction.[25] In five cases, the cord lesions were indicated by blue staining, and only small perivascular hemorrhages were present. The cord lesions usually involved multiple segments and overlapped some

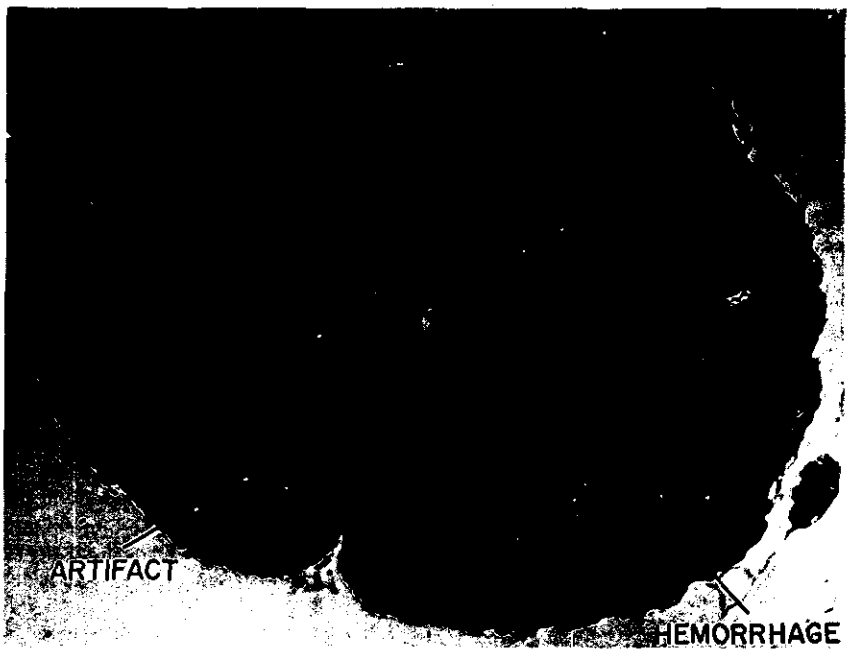

Figure 5. Cross section of canine cervical cord showing white matter hemorrhage and gray matter sparing.

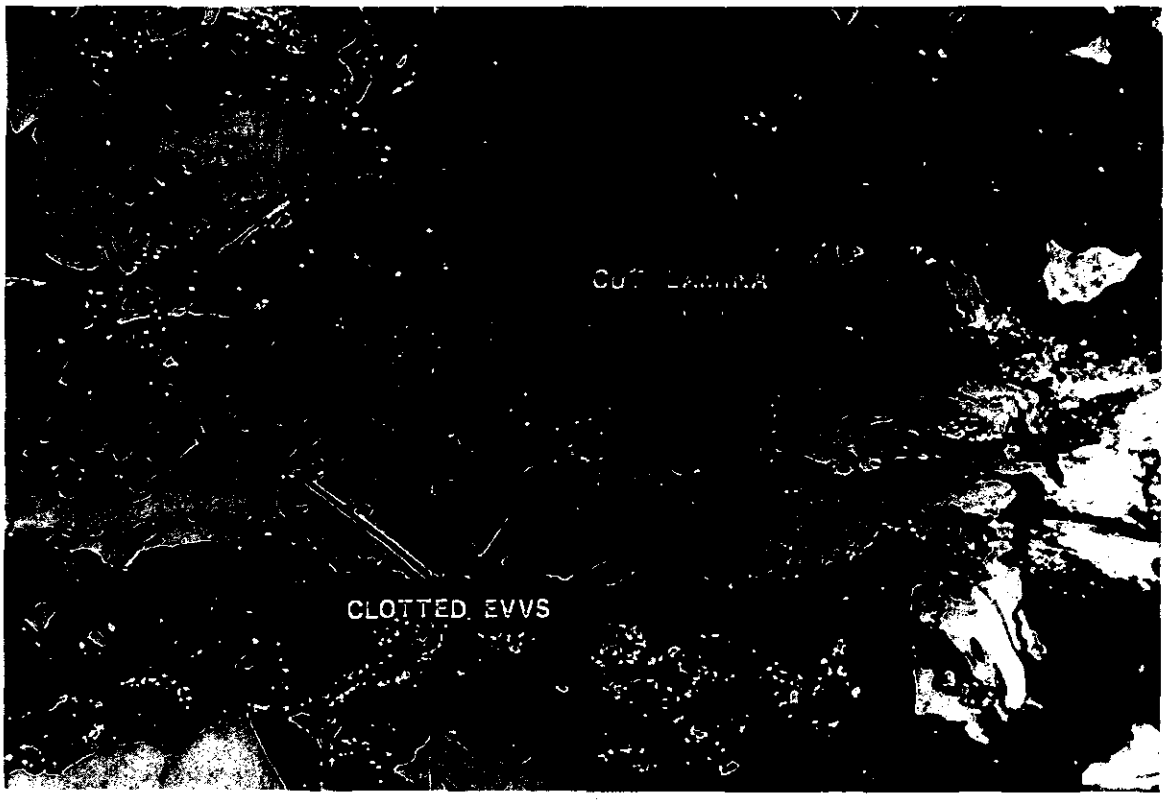

Figure 6. Clots in the epidural vertebral venous system (EVVS) of a dog with spinal cord damage secondary to decompression sickness. The spinal canal has been unrooted and the spinal cord has been removed. The dark areas on both sides of the spine are dissected paravertebral muscles.

combination of cervical, thoracic, and lumbosacral regions. However, in three animals, the lesions were confined to several thoracic segments, and in two animals, only several cervical segments were involved. Subarachnoid hemorrhage often occurred when the cord lesions were grossly hemorrhagic. Hemorrhages in the epidural fat, corresponding to levels of gross hemorrhage in the cord, were the rule. Small clots were frequently observed in regions of the epidural vertebral venous system of paralyzed dogs at autopsy, and in five cases the clotting was extensive (figure 6).

A normal brain was found in the dog exposed to severe decompression sickness in the supine position in order to minimize the possibility that systemic bubble emboli could be carried to the cord by buoyancy in blood. However, there were widespread and severe hemorrhages in the spinal cord white matter, with remarkable sparing of the gray matter. The pathologic picture was again that of venous cord infarction.

Discussion. The results indicate that during the course of severe decompression sickness leading to spinal cord damage, regions of the epidural vertebral venous system become obstructed. The results strongly suggest that venous obstruction at this level and the consequent impairment of cord venous drainage have a causal role in the production of spinal cord lesions in decompression sickness.

It is difficult to envision bubbles obstructing vessels as large as those constituting the epidural vertebral venous system without a clear understanding of the anatomy and physiology of the system. The epidural vertebral venous system of the dog consists mainly of paired trunks extending from skull to sacrum within the spinal canal.[26] In man, the epidural system is more plexiform and is connected at each intervertebral foramen with ascending lumbar veins in the abdomen, with azygos and hemiazygos veins in the thorax, and with vertebral veins in the neck.[27] The epidural vertebral venous system also communicates with cranial dural sinuses via ventral occipital sinuses and with posterior bronchial and parietal pleural veins.

The epidural vertebral venous system of man, as discussed by Batson,[28–30] is a large valveless venous lake in which there are frequent changes in the direction of flow in response to respiration and changing intracavitary pressures. Indeed, Clemens[31] states that the volume of the system is some 20 times greater than that of the arteries supplying the regions it drains, so that only about 5 percent of the epidural vertebral venous system blood volume needs to be flowing at any one time. Radicular veins drain the spinal cord into the epidural vertebral venous system, and venous drainage of the spinal cord, like its arterial supply, is nonsegmental and rather tenuous.[32] The epidural vertebral venous system thus differs from other veins in that it is not simply a unidirectional conduit transporting blood toward the heart but is instead a relatively stagnant pool in which the rate of flow is ordinarily sluggish and the direction of flow changes frequently. The epidural vertebral venous system can become obstructed by bubbles that collect, coalesce, and grow, when other major veins do not become obstructed, precisely because of the system's function as a valveless venous lake. By analogy with water freezing, lakes freeze and rivers do not.

We feel that the following general overview is consistent with existing knowledge. Initially, bubbles arise peripherally in regions of the systemic microcirculation and interstitial spaces, where they begin to exert direct mechanical effects and also indirect effects due to surface activity at gas-blood interfaces. The gas-blood interface as discussed by Lee and associates[33,34] is a 40-100 A zone of electrokinetic forces that tend to alter the secondary and tertiary configuration of blood proteins, leading to activation of the clotting system, platelet aggregation, release of vasoactive substances, and disturbance of blood rheology due to plasma loss and red cell clumping.

Depending on the extent of bubble nucleation, the process could follow one of several courses. Elimination of gas, bubble resorption, and inactivation of products of bubble surface activity could cause the process to subside. Failing this, the process could continue as a local phenomenon and reach the clinical horizon as perhaps pain in the region of a joint, a limb-bend. In more extreme cases, many bubbles and products of bubble surface activity would enter the larger veins and migrate to the lungs. This causes an acute rise of pulmonary artery pressure.[23] Concurrently, the cyclic fluctuations of intrathoracic pressure that accompany respiration increase in amplitude, becoming more negative during inspiration and more positive during expiration. These changes are followed by central venous congestion and a rise in central venous pressure that is reflected back into the epidural vertebral venous system, causing stasis and congestion. Bubbles in this venous reservoir then can grow and coalesce, leading ultimately to regional obstruction. The bubbles activate the hemostatic process,[35] and if stasis is maintained for about the length of silicone clotting time of the blood,[36] fibrin deposition occurs, reinforcing and perpetuating any obstruction. When the epidural vertebral venous system is blocked at the point of drainage of a critical radicular vein, the resulting interference with spinal cord venous drainage synergizes with the generalized rheologic disturbance attending severe decompression sickness[37] to produce an area of infarction.

Whereas the foregoing pathophysiologic sequence is consistently seen following dives that produce early and severe decompression sickness in dogs, recent studies suggest that acute pulmonary hypertension and central venous congestion are not absolutely essential for bubble obstruction of the epidural vertebral venous system to occur. Experiments in progress involving laminectomized dogs subjected to a less severe dive profile (220 ft for 25 minutes) demonstrate that after a latent period of 20 minutes or more, the epidural vertebral venous system can become occluded with bubbles without any preceding pulmonary hypertension or central venous pressure rise. This is very interesting because

clinical experience with human decompression sickness cases indicates that pulmonary symptoms are often mild or absent and that spinal cord dysfunction can present as an isolated symptom. It would appear, then, that a dive that exceeds safe decompression limits by a large margin will cause acute pulmonary hypertension, central venous congestion, and early obstruction of the epidural vertebral venous system, but that delayed epidural vertebral venous system obstruction can occur in the absence of central vascular pressure changes when the omitted decompression is not extreme.

Authors' note

The opinions or assertions contained herein are those of the authors and do not necessarily reflect the views of the Navy Department or the naval service at large. The animals used in this study were handled in accordance with the provisions of Public Law 89-44 as amended by Public Law 91-579, the "*Animal Welfare Act of 1970*," and the principles outlined in the "Guide for the Care and Use of Laboratory Animals," U.S. Department of Health, Education, and Welfare Publication No. (NIH) 78-23.

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HANDBUCH DER SPEZIELLEN PATHOLOGISCHEN ANATOMIE UND HISTOLOGIE

HERAUSGEGEBEN UNTER MITARBEIT
HERVORRAGENDER FACHGELEHRTER

VON

O. LUBARSCH
BERLIN

F. HENKE
BRESLAU

R. RÖSSLE
BERLIN

DREIZEHNTER BAND

NERVENSYSTEM

HERAUSGEGEBEN VON

W. SCHOLZ
MÜNCHEN

ERSTER TEIL
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SPRINGER-VERLAG
BERLIN · GÖTTINGEN · HEIDELBERG
1957

IV-15-105

NERVENSYSTEM

ERSTER TEIL

ERKRANKUNGEN DES ZENTRALEN NERVENSYSTEMS I

BEARBEITET VON

G. BODECHTEL · A. VON BRAUNMÜHL · ST. COBB
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MIT 356 ZUM TEIL FARBIGEN ABBILDUNGEN

SPRINGER-VERLAG
BERLIN GÖTTINGEN HEIDELBERG
1957

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Decompression sickness.

By

Webb Haymaker - Washington, D. C.

With 27 illustrations.

I. Etiology and pathogenesis.

A. Nitrogen supersaturation and bubble formation.

1. General considerations.

The principles underlying the development of decompression sickness in ascents to altitude and from increased atmospheric pressure have much in common. Rapidity of decompression is of paramount importance in both, for if the ambient pressure with which the tissues are in equilibrium is reduced too quickly the gases in the blood stream and tissues become supersaturated and under appropriate conditions vaporize. N_2 is the gas chiefly concerned, for it is physiologically inert and thus goes into simple solution in the body tissues and fluids in an amount proportional to its partial pressure. If during decompression from increased atmospheric pressure the concentration of N_2 in the body becomes more than 2.25 times its normal saturation value at any atmosphere-pressure, the N_2 will form bubbles to which are added O_2, CO_2 and H_2O vapor (BEHNKE et al. 1940; HALDANE and PRIESTLEY 1935).

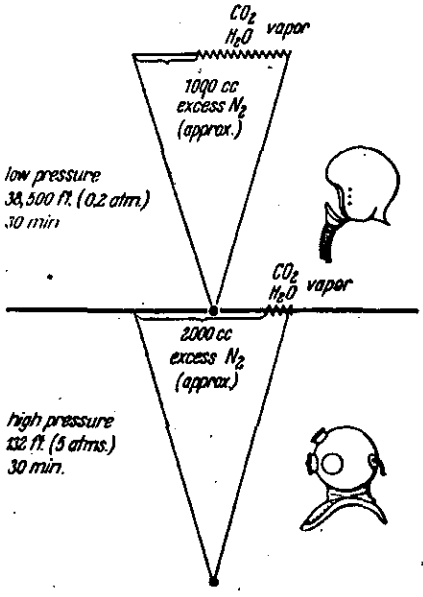

Fig. 1. The gases contributing to bubble formation in diving versus altitude decompression. (Courtesy of A. R. BEHNKE.)

In ascent to altitude a fall in barometric pressure to about one-third the ground pressure is necessary before symptoms of decompression sickness develop, i.e., at about 25,000 ft. (7,620 m.). On the other hand, BEHNKE et al. (1940) have concluded that the critical level at which manifest bubble formation occurs is about 20,000 ft. (6,100 m.), and they commented that: "It may well be that bubbles form as soon as a state of supersaturation is initiated and that what appears to be a ratio of saturation tolerance is in reality an index of the degree of embolism that the body can tolerate." According to this figure, the threshold decompression ratio would be 760/345, or 2.20. This value is virtually the same

as in decompression from increased atmospheric pressure, which, as mentioned in other terms, is 2.25. Evidence has been cited that "silent" bubbles may form even on decompression to an altitude of 15,000 ft. (4,570 m.) (BATEMAN 1951).

Crucial in the causation of decompression sickness is the quantity of gas which must be released at the tissue level. BEHNKE (1955) has shown that for a 70-kilogram individual who has spent 30 minutes at 5 atmospheres (132 ft.; 40 m.), approximately 2,800 cc. of gas must be released at the tissue level during decompression to 1 atmosphere, and of this quantity, *2,000 cc.* are N_2 and 800 cc. O_2 and H_2O vapor. For the same individual who is decompressed from 1 atmosphere to 0.2 atmosphere (38,500 ft.; 11,700 m.), the same quantity of gas is given off, but only *1,000 cc.* of it is N_2 and the remainder, CO_2 and H_2O vapor (Fig. 1).

2. Nitrogen clearance.

The clearance rate of a dissolved inert gas from a tissue is directly proportional to the blood flow per gram of tissue and inversely proportional to the solubility of gas in the tissues. This may be expressed in the following equation:

$$k \text{ (clearance rate)} = \frac{F}{W\lambda}$$

where F signifies the blood flow per unit weight of tissue, and λ the ratio of tissue over blood solubility of the gas (KETY 1951).

No significant relationship has been found to exist between susceptibility to decompression sickness and the rate at which N_2 is cleared from the blood when O_2 is breathed, for the reason that the rate of N_2 clearance from the lungs represents a composite of the clearance rates of all body tissues, a value which does not vary significantly from individual to individual (FRASER 1942; STEVENS et al. 1943, 1945). On the other hand, the various body tissues have different susceptibilities to gas bubble formation because N_2 is cleared more rapidly from some tissues than from others, depending on the amount of N_2 stored (which is determined by tissue composition) and vascularization (as stated in the equation) (EGGLETON et al. 1945; LAWRENCE et al. 1948; WHITELEY and MCELROY 1946). The blood perfusion gas exchange rate of the brain is relatively high, as has been observed by KETY and SCHMIDT (1945) (N_2O measurements) and JONES (1951) (radio-xenon measurements). An important factor in the speedy gas exchange is the relatively low N_2 solubility in the brain. In this respect the brain is no different from non-fatty tissues (CAMPBELL and HILL 1931, 1933). JONES (1951) has estimated that the brain is virtually equilibrated to the changing inert gas concentration in the lungs in 6 to 7 minutes after the change in lung tension has been effected, from which he concluded that during *decompression to altitude* the brain is relatively protected from supersaturation of dissolved gas. On the other hand, in *compression* the vascularity of the brain is such that in the course of about 10 minutes the brain becomes 90% equilibrated with the pulmonary N_2 tension. The same applies to other richly vascularized organs such as the liver, kidney, and heart. By contrast, fat tissue (including fatty bone marrow) has a slow gas exchange, N_2 saturation occurring, according to BOYCOTT et al. (1908) in 5 hours, and according to BORNSTEIN (1910, 1914) in 8 to 10 hours. Thus, if at the end of 10 minutes' compression, rapid decompression is carried out—when saturation has occurred in the brain but not in the tissues—it would be expected that the brain would be much more subject to N_2 bubble formation than fat. This would, however, occur only if the capacity of the circulation to carry N_2 away from the brain (or, for that matter, the liver,

kidney, and heart) could be exceeded. On the other hand, if rapid decompression is carried out after prolonged compression, the fat would be much more subject to N_2 bubble formation because of the comparative slowness of its N_2 clearance.

3. Sites of formation and growth of gas bubbles.

The numerous studies by HARVEY et al. (1944, 1945) have indicated that gas bubbles arise both intravascularly and within tissues. According to their view, the bubbles developing intravascularly arise from gas nuclei which appear on or within the endothelial lining of the vascular system; those forming in tissues may originate from gas nuclei or they may result from exercise when the forces exerted open up spaces in the fluids into which sufficient gases diffuse to remain in the form of a bubble after the strain is relieved. This "strain" theory of bubble genesis has numerous proponents (EVELYN 1941; MCELROY et al. 1944; FERRIS et al. 1943).

Others advocate what may be referred to as the "work" theory (BERG et al. 1945; HARRIS et al. 1945; HENRY 1945, 1946; WHITAKER et al. 1945). According to this theory, muscular contraction increases CO_2 concentration to a degree sufficient to cause supersaturation of the gas, and, as a consequence of mechanical tension, bubbles consisting chiefly of CO_2 form very rapidly. Much of the CO_2 is subsequently eliminated by diffusion in the blood stream and is replaced by N_2, upon which "permanent" bubble growth depends. Lactic acid also has a facilitating action on bubble formation (BEHNKE 1951). In analyzing the data on which this theory is based, COOK (1951) stated that

> "If CO_2 has an importance commensurate with that ascribed to it ... then the effect of exercise may be regarded as quantitative rather than qualitative. The lactic acid and the CO_2 production will be proportional to the amount of exercise or the amount of physical work performed and the concentration of bends symptoms in the active regions will be the result of local high tension of CO_2."

In studies carried out during routine dives in a 100-foot-deep submarine escape training tank, SCHAEFER (1954) observed that at the end of dives of approximately 2 minutes' duration, which included descent to and ascent from 90 ft. (27.5 m.), the alveolar gas concentrations were as follows: 5—6% O_2, 5—6% CO_2, and 88—90% N_2. (The CO_2 values were obtained by means of HALDANE's sampling technique or through the use of an infra red CO_2 recorder.) Immediately after ascent from 90 ft., arterial and venous blood was withdrawn simultaneously from the two arms. The first 2 cc. of both arterial and venous blood were foamy, whereas the succeeding blood drawn into the syringe was foam-free. The explanation offered for the unexpected low CO_2 concentration and the 10% increase in N_2 concentration of the alveolar air at the end of the dive was that N_2 had been relatively quickly released from small stores (i.e., that only in physical solution), whereas CO_2 had been relatively slowly released from large stores (i.e., from that in physical solution and that combined with a large quantity of buffers). The bubbles observed in the first 2 cc. of blood were thus thought to be N_2 bubbles. It seems plausible to assume that the bubbles developed only after the N_2-overladen blood came into contact with the surface of the syringe. On the basis of these observations, SCHAEFER has expressed the opinion that although CO_2 may facilitate bubble formation in the blood stream and tissues, the bubbles are composed initially of N_2.

That gas bubbles may form in the *spinal fluid* as the result of decompression has been clearly shown in goats by ARMSTRONG (1952). A spinal puncture needle was inserted into the cisterna magna and connected with a water manometer. The animals were placed in an altitude chamber, fitted with O_2 masks, and

exposed to various pressures. At 18,000 ft. (5,500 m.) the pressure of the spinal fluid began to increase and at the same moment gas bubbles appeared in the spinal fluid in the manometer. As ascent continued, the bubbles increased in number, then decreased, and then they vanished. Similar observations were made by ARMSTRONG and BENSON (cited by WALSH 1941), on a human volunteer, and by WALSH (1941) on 3 human volunteers. Bubbles, which were fine "champagne-like"—but intermixed with some larger bubbles, appeared in the manometer at a simulated altitude of 10,000 to 12,000 ft. (3,000 to 3,600 m.). The bubbles became larger and more numerous at altitudes up to 28,000 ft. (8,500 m.) and after approximately 5 minutes' exposure to such "altitudes" the bubbles decreased in number and size and shortly disappeared. The conclusion reached was that the bubbles probably were similarly given off in the spinal fluid in situ.

4. Protective mechanisms of diving animals and human beings during decompression.

Air-breathing animals are known to stay at considerable depths for a relatively long time and to return to the surface without developing decompression sickness. Thus, beavers can stay under water for 15 minutes (IRVING and ORR 1935), seals for 25 minutes (AMOROSO 1954), and bottle-nosed whales can remain submerged at about 3000 ft. (915 m.) for as long as 2 hours (IRVING 1939). Underwater sojourn is made possible by respiratory and circulatory adjustments (IRVING 1939; SCHOLANDER [cited by KROGH 1941]). As to *respiratory adjustments*, SCHOLANDER has pointed out that seals and whales have small lungs with a large dead space in the bronchi and trachea which has a capacity $^1/_{10}$ the lung volume. Before a dive the animal exhales, and by the time the animal reaches 130 ft. (40 m.) the N_2 in the lungs has been forced into solution in the tissues. By the time a depth of 330 ft. (100 m.) is attained, any air which had remained in the lungs would have been displaced into the dead space by the increasing ambient pressure. Consequently at this depth, diffusion of N_2 and O_2 cannot occur. Whales have large stores of O_2 (large blood volume, high concentration of blood hemoglobin, and abundant muscle hemoglobin) and they are much less sensitive to the accumulation of CO_2 than non-diving animals (IRVING and ORR 1935; SCHOLANDER [cited by KROGH 1941]). This decreased sensitivity during a dive may be due to storage of CO_2 in the spinovertebral and associated venous plexuses, which, in the seal at least (AMOROSO 1954), is extraordinarily rich. The *circulatory adjustment* during a dive consists in an extreme slowing of the heart rate. When a seal dives, its heart rate falls from 120 to as low as 10 (SCHOLANDER [cited by KROGH 1941]). Reduction of blood flow occurring in association with the bradycardia would further decrease the distribution of gas.

A comparison of the diving capacity of human beings and diving animals has been drawn by SCHAEFER (1954). The studies on human beings were carried out in a 100-foot-deep submarine escape training tank, with diving instructors as the subjects. Observations were made on 1. the alveolar CO_2 and O_2 tensions, 2. pulse rate, 3. metabolism before, during and after free dives to 90 to 100 ft. (27.5 to 30.5 m.), and 4. the ventilatory responses to low O_2–N_2 mixtures and CO_2 mixtures. Like diving animals, efficient divers were found to have a decreased sensitivity to CO_2, an adaptation to low alveolar O_2 and a low respiratory rate, but unlike diving animals they had an increased lung capacity (increased respiratory reserve).

5. Sites of circulating and autochthonous gas bubbles.

In severe decompression sickness, bubbles are found both in arteries and in veins. N_2 bubbles developing as a result of too-rapid decompression quickly disappear from the arterial blood stream because of the high arterial pressure and the rapid equilibration of the venous blood with alveolar air (HORNBERGER 1950). Under conditions of moderate decompression they are most abundant in veins (during exercise especially in veins draining muscle masses [WHITELEY and MCELROY 1946]) because of the low venous pressure and the facilitatory action exerted by CO_2 tension on the growth of gas bubbles. Whether in the blood or in the tissues, bubbles tend gradually to disappear because the partial pressures of their gases exceed the partial pressures of the gases in the surrounding milieu.

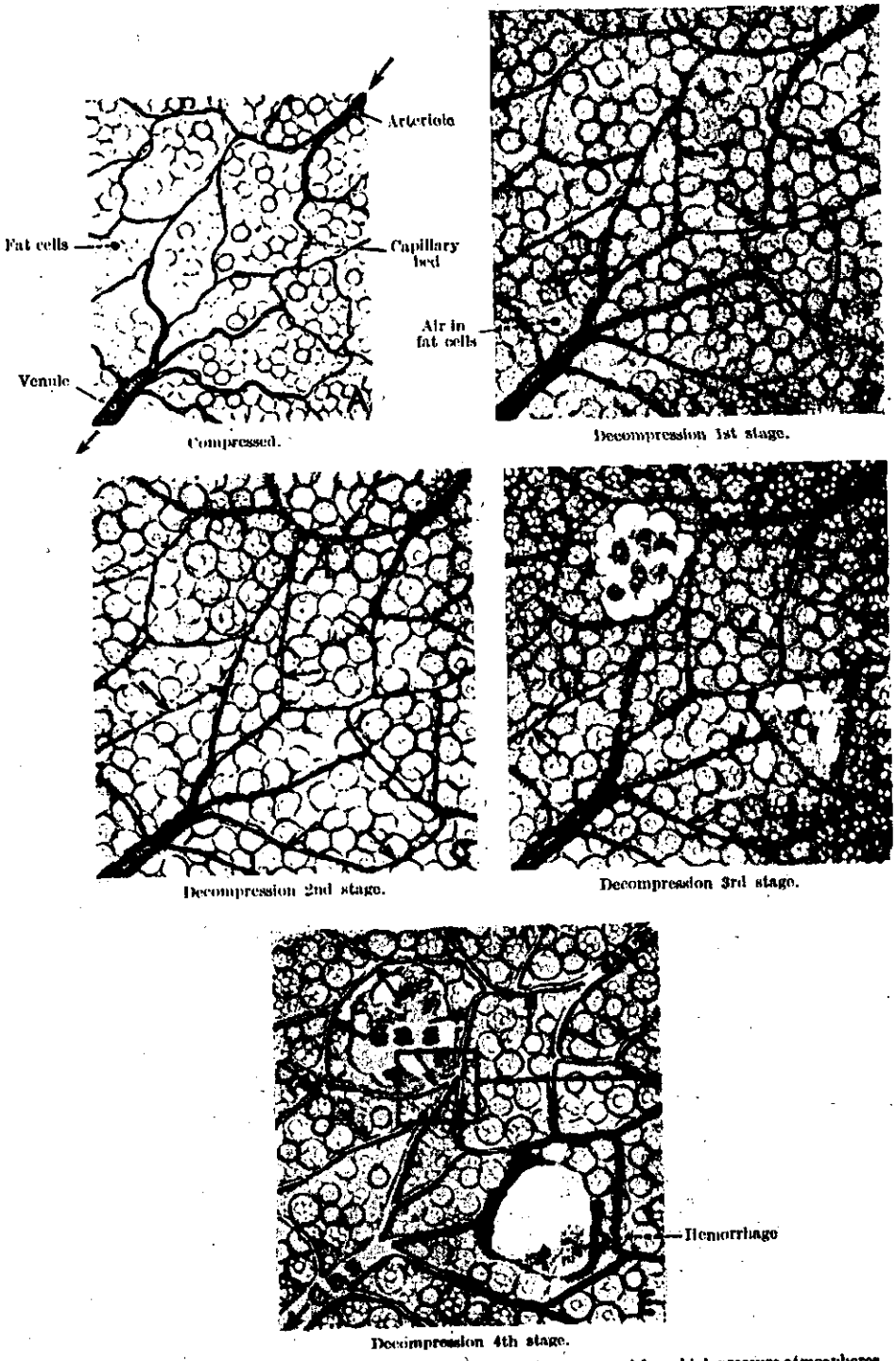

Fig. 2 A–E. Postulated changes in fat tissue of guinea pigs decompressed from high pressure atmospheres. A Fat cells are rich in dissolved N_2 during compression. B On decompression the fat cells enlarge as a consequence of the growth of tiny intracellular bubbles. As indicated by the arrows, the gas in solution passes from the bubbles into the tissue fluid and blood stream where it may remain dissolved or form bubbles. C In some regions the cells increase in size as a result of continued growth of intracellular gas bubbles. D Some cells rupture and discharge their contents into an irregularly outlined intercellular or extravascular bubble which contains cellular debris, fat, and gas under pressure. E Rupture of blood vessels and hemorrhage may also occur. The mode of passage of gas from the fat to the blood vessels is not known, but continuity of the gaseous tissue bubbles with vascular channels is possible. (From GERSH and HAWKINSON 1944a; also in GERSH et al. 1944b.)

The sites at which gas bubbles have been found post mortem in animals and human beings subjected to a rapid change in barometric pressure has varied. Following decompression from *increased pressure atmospheres*, Boycott et al. (1908) and Hill (1912) have noted gas bubbles in fat tissue, liver, kidney, and spinal cord. Through the freezing-drying method, which preserves bubbles *in situ*, though it does not guarantee against the formation of ice crystals in tissue, Gersh et al. (1944a and b) have observed in guinea pigs very rapidly

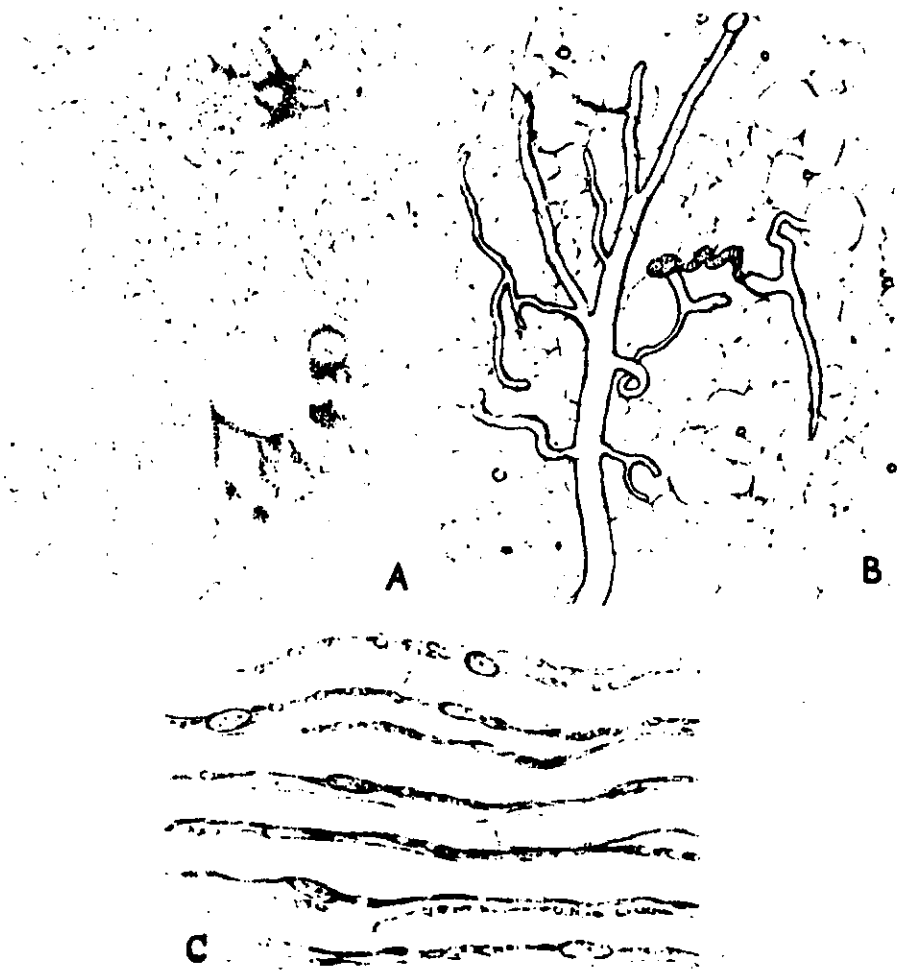

Fig. 3 A—C. Camera lucida drawings of fat tissue and an idealized drawing of peripheral nerve of guinea pig decompressed from high atmospheric pressures. A Petechiae in fat tissue in the vicinity of extravascular bubbles. B Venous capillaries distended with gas and an arteriole (stippled) which is constricted at one end and filled with erythrocytes at the other. C Tiny bubbles in the myelin sheath of nerve fibers of the sciatic nerve. (From Gersh and Hawkinson 1944a; also in Gersh et al. 1944b.)

decompressed from high pressure atmospheres that bubbles develop extravascularly in fat tissue, adrenal cortex, and peripheral nerves, but not in spinal cord, skeletal muscle, tendon, or liver (Figs. 2 and 3). In animals sacrificed after rapid decompression from prolonged compression (3 hours), numerous gas bubbles were found in the lungs intraarterially, in the spleen intravascularly (sinusoids, arteries, veins—in that order of frequency), and in the bone marrow both intravascularly (arteries, veins and sinusoids) and extravascularly (Gersh 1945).

In rabbits *decompressed to an altitude* of 45,000 ft. (13,700 m.) in 4 seconds to 4.8 minutes and autopsied at 30,000 ft. (9,140 m.), Gersh and Catchpole (1946) found in the frozen-dried tissues that the occurrence of gas bubbles was very similar to that in guinea pigs decom-

pressed from depth when the depth selected for comparison was the lowest lethal one (60 lb. per sq. in.). In both groups of animals gas bubbles were present in the right side of the heart, in the arterial tree of the lungs (many in the high pressure animals, few in the low pressure animals), in arteries and veins throughout the body, in capillaries of fat tissue, and in sinusoids of the spleen. As to extravascular gas bubbles, they were present in fat (intracellular) and in the adrenal gland in animals decompressed from high pressure but not in those decompressed to altitude. In neither group were gas bubbles found in nerves (except in fat of the epineurium and in vessels) or in liver sinusoids. In the animals decompressed to altitude, bubbles were "perhaps" present in bone marrow sinusoids. Hemorrhages in fat tissue were rare. No data on the CNS were given. When bubbles were scarce in peripheral vessels, they were nearly always present in small numbers in the inferior vena cava and right heart, and when bubble population was minimal, the bubbles tended to be confined to veins. On the other hand, in those animals overwhelmed with bubbles they were present both in arteries and veins.

6. Symptom-producing capacity of local gas bubbles.

The symptom-producing capacity of gas bubbles in the tissues varies, depending on location and circumstance, but, as brought out by NIMS (1951), the degree of deformation pressure exerted by bubbles is of paramount importance in the development of pain and other symptoms. It is the magnitude of the distortion pressure, not the size of bubbles, that counts. Gas bubbles growing in tissues displace and deform adjacent tissues—influences which the tissues tend to resist by virtue of their elasticity. Pressure from bubbles growing in the CNS may be sufficient to block conduction in the nerve fibers and thus add to the disability brought about by the parenchymal ischemia induced by gas bubble embolization. But deformation has still other potentialities. When it is excessive, the involved tissues give way, limiting membranes may be torn, and cells destroyed. Such trauma has been considered an important cause of secondary (delayed) shock (pp. 1612—1613, 1629, 1643).

B. Other factors in the development of decompression sickness.

Many factors are concerned in susceptibility to decompression sickness. The influence of exercise on the growth of gas bubbles has been discussed in the foregoing. Age is also of significance since it influences the circulation of the blood and hence the rate of transport of gas from the tissues (BECKER-FREYSENG [cited by HORNBERGER 1950]); BOYCOTT et al. 1908; GRAY 1951; HILL 1912; SMITH 1942; STEWART et al. 1943). Degree of fatness is also of fundamental importance.

Obesity and rate of respiratory exchange.

That obese individuals have a predilection to decompression sickness has been known for many years. As early as 1868, de MÉRICOURT recommended that no corpulent individual be employed as a sponge fisherman. Years later, BOYCOTT and DAMANT (1908) reached the same conclusion with respect to caisson workers. In some aviation circles in the U.S.A. today no individual who is more than 10 pounds overweight is subjected to indoctrination runs in decompression chambers.

At normal blood temperature the body fat dissolves 5 to 6 times as much N_2 per unit mass as does the blood (VERNON 1907; HILL 1912), and during and directly after decompression, the N_2 in the fat—in contrast with that in the blood, which is quickly equilibrated with the atmospheric pressure—remains under tension and thus serves as a N_2 reservoir. In this connection, tissue bubbles have been found to develop much more readily in fat than in lean animals during

decompression (GERSH et al. 1944b) and it has been noted that the fatter the *animal the more rapid the bubble formation* (HARVEY et al. 1944).

Obesity as a hazard in *decompression to altitude* has also been substantiated. In an analysis of the data on some 48,000 Air Force trainees in which linear density (weight/height) was used as an index of obesity, GRAY (1951) noted a significant increase in susceptibility with increase in linear density. In the range from 2.0 to 3.0 linear density, relative susceptibility increased approximately 3-fold.

By way of contrast, in animals decompressed to altitude, HARVEY et al. (1944) found little correlation between estimated "total fat" content of the body and the time of the appearance of the first intravascular gas bubbles. Their observations, made on cats, were *based on the time of appearance of bubbles in the postcava after electrically-induced muscular* contraction of the hind limb. Only when the bubble formation was relatively slow, as in decompression from critical excess air pressures, was a correlation between fat and bubble production observed. In confirmation were the observations on rabbits by CATCHPOLE and GERSH (1946) that no correlation exists between fatness and the time of the first appearance of gas bubbles, the severity of symptoms, or the time of survival. Their studies were based on the appearance of bubbles in the vena cava after decompression to 45,000 ft. (13,700 m.) over a period of 3 seconds to 10 minutes, with O_2 being supplied by a tracheal cannula. "The implication is, that in animals decompressed to altitude, fat as a gas reservoir contributing to total bubble population is relatively unimportant, due either to the small amount of gas dissolved in it compared with that in fat of animals under pressure, or to mechanical blockage of vessels by bubbles which then fail to enter the general circulation." *Death in these animals was regarded as probably due to gas bubble embolism of the* CNS. According to HARVEY et al. (1944), obesity favors susceptibility to decompression because of the capacity of fat to dissolve comparatively large amounts of N_2 and because fat has a low respiratory exchange per unit of body weight.

C. Cardiac embarrassment and pulmonary embolization.

1. In decompression sickness.

Almost a century ago, HOPPE-SEYLER (1857) found gas bubbles circulating in large veins of animals decompressed either from high pressure atmospheres or from ground level to a simulated 62,000 ft. (18,900 m.). He attributed death under these circumstances to the occlusion of pulmonary capillaries by gas bubbles, and reasoned that some of the difficulties occurring in divers and caisson workers are due both to blockage of pulmonary vessels by gas and to an inability of the heart to propel blood through the lungs. HOPPE-SEYLER's observations were, in a way, in confirmation of those of BOYLE, who, in 1670, subjected animals to a rapid reduction of atmospheric pressure by creating a vacuum around them, only to find that

"upon the withdrawing of the Air, besides the removal of what the Airs presence con*tributes to life, the little Bubbles generated upon the absence of Air in the Blood, juyces,* and soft parts of the Body, may by their Vast number, and their conspiring distension, variously streighten in some places, and stretch in others, the Vessels, especially the smaller ones ... and so by choaking up some passages ... disturb or hinder the due circulation of the Bloud ... I once observed in a Viper, furiously tortured in our Exhauster Receiver ... that it had manifestly a conspicuous Bubble moving to and fro in the waterish humour of one of its Eyes."

HOPPE-SEYLER and BOYLE thought that the bubbles they saw were composed of N_2 or air, a conclusion reached also by HILL and GREENWOOD (1909) from their observations on a rabbit decompressed rapidly to a simulated altitude of approximately 63,000 ft. (19,200 m.). There is every probability, however, that the bubbles consisted of H_2O vapor, for this height is the critical level at which blood vaporizes en masse (ARMSTRONG 1952).

Considering the problem of cardiac and respiratory embarrassment under lower magnitudes of *decompression from increased atmospheric pressure*, BEHNKE et al. (1936) noted that when dogs were exposed to an atmosphere of 60 pounds gauge pressure for 1½ hours and then were rapidly decompressed, they showed no ill effects until ½ hour later, when their breathing became rapid and shallow. Coincident with the increase, bubbles were seen moving through cutaneous arteries and veins, and gradually increasing in size and slowing and eventually halting the circulation.

The rapid, shallow breathing in the early stages of the asphyxia was considered by BEHNKE and SHAW (1937) and BEHNKE (1945) to be primarily the result of reflex stimuli initiated in the pulmonary vessel walls by alternate distention and contraction during inspiration and expiration respectively. The systolic blood pressure rose to 140 mm. Hg, but later fell rather precipitously to 40 mm. Hg. In due time the pulse rate also fell. The temporary rise in blood pressure was ascribed to increased peripheral resistance brought about by widespread vascular occlusion by gas bubbles, and the abrupt fall chiefly to retardation of blood flow to the left ventricle as a consequence of filling of the pulmonary circuit with gas bubbles. The maintenance of life under these conditions was considered to be dependent on the functional integrity of the right ventricle, i.e., its ability to propel blood through the obstructed pulmonary bed.

In dogs rapidly decompressed from an atmosphere of 60 pounds to which they had been exposed for 1½ hours, and again compressed at the same gauge pressure for 2 hours and then rapidly decompressed, BEHNKE et al. (1936) found that gas bubble formation was of sufficient magnitude to fill the right ventricle and cause immediate asphyxial death. The acute asphyxia thus induced was not preceded by tachypnea. Thus, BEHNKE et al. demonstrated that whereas gas bubble embolization of moderate degree led predominantly to pulmonary disturbances, in massive embolization the brunt of the insult was borne by the heart.

The view that large quantities of gas bubbles reaching the right ventricle may be churned into a froth, preventing the ventricle from delivering its blood to the lungs, has led to the practice in the Swedish submarine service of aspirating the foamy blood from the heart of divers who have reached the surface in extremis (SCHERSTÉN 1948).

In *decompression to altitude* the same principles with respect to N_2 bubble formation apply, but here the hazard of cardiac embarrassment and pulmonary embolization is less because of the smaller quantity of undissolved gas in the body. In rabbits decompressed to 45,000 ft. (13,700 m.) for 3 to 30 minutes and autopsied at 30,000 ft. (9,150 m.), CATCHPOLE and GERSH (1946) found very few bubbles in the pulmonary and coronary arteries. They postulated, therefore, that death was due to CNS gas bubble embolism, the variability in time lapse before death being dependent on chance lodgement of bubbles in vessels in vital parts of the CNS.

2. In venous air embolism.

Many of the observations made on air embolism support and supplement those referred to in the foregoing pages. Since air gaining the blood stream quickly loses its O_2, one may assume that the bubbles circulating in the blood consist chiefly of N_2. The only important difference, therefore, between air emboli and the N_2 emboli arising as a result of decompression is that the air emboli come from a circumscribed region of the exterior, often as a single mass of air, whereas the N_2 bubble emboli flow from myriad venous tributaries over a variable period of time.

BERGSTRAND (1924) expressed the view that air bubbles reaching the pulmonary arterial tree tamponade the arterioles and thus lead to elevation of intrapulmonic arterial pressure and lowering of the pressure in the left heart and aorta. Dyspnea, cyanosis, coma and sometimes convulsions occurred, and death also if the carotid blood pressure fell sufficiently to produce serious cerebral ischemia. According to DURANT et al. (1947) the clinical characteristics of pulmonary (venous) air embolism in man include a "mill wheel" murmur in the heart, increased venous pressure, lowered arterial pressure, rapid and thready pulse, and syncope due to CNS ischemia. Death, if it occurs, is rapid.

HASELHORST (1924), GORET and GILLARD (1934) and MARTLAND (1945) also believed that obstruction of the pulmonary arteriolar tree was the basic disturbance in venous air embolism. FREY (1927) and NEUMEYER (1936) were inclined toward the same view that death was due to asphyxia from pulmonary embolization, on the basis that the heart continued to beat after respiration had ceased. In this connection, HAGGART and WALKER (1923) estimated that 55 to 66% occlusion of the pulmonary arterial tree is necessary before the general circulation is embarrassed.

On the other hand, WOLF (1903) contended that filling of the pulmonary arterial tree by a frothy mixture of air and blood raises the pressure in the right ventricle and thus strains the ventricle to the point of failure and standstill. Observing few or no functional disturbances after the injection of air into the pulmonary artery, KLEINSCHMIDT (1915) concluded that death in air embolism is due to right heart failure incident to the presence of air in the heart. Frothy blood is more compressible than normal blood and less readily expelled from the heart, so that much of the air remains in the heart after every systole. JEHN and NAEGELI (1918) concurred in KLEINSCHMIDT's view, but felt that reduction of blood flow to the left side of the heart contributed to the cardiac failure. DURANT et al. (1947) have observed in dogs with the heart exposed that almost immediately after the injection of 25 to 150 cc. of air into the femoral vein, the right auricle and ventricle become strikingly dilated and the venous pressure rises. Simultaneously an area of the right ventricle just to the right of the lower region of the anterior descending branch of the left coronary artery became strikingly ischemic. By means of transillumination a large air bubble was found subjacent to the ischemic area. EKG tracings taken from the ischemic area disclosed severe functional disturbances. If before the right cardiac dilation became extreme the animals were turned on their left side, causing the air bubble in the right ventricle to disappear, the contractions of the right ventricle again became strong and the animals recovered. [The same has been observed in man by HAMBY and TERRY (1952).] Referring to the rationale of cardiac failure as expressed by VISSCHER (1939), DURANT et al. concluded that the right ventricular ischemia was due to a pronounced retardation of the thebesian flow as a consequence of the increased right ventricular pressure. This retardation together with the decrease in aortic pressure combined to reduce profoundly the aortic-right ventricular pressure gradient so that blood flow of the muscle of the right ventricle was impaired, causing ischemia.

Death in pulmonary (venous) air embolism has been ascribed to various factors. The amount of air introduced is of importance. RICHARDSON et al. (1937) estimated that the upper limit of tolerance for man under ideal conditions is approximately 80 cc. Plotting a rate-mortality curve from the results of RICHARDSON et al., CATCHPOLE and GERSH (1946) found that it roughly paralleled the survival trend of rabbits decompressed at various rates. With respect to speed of air injected, the lethal volume of air has been found to be inversely related to the speed at which air is introduced (GORET and GILLARD 1934; PINES 1939; RICHARDSON et al. 1937; SCHLAEPFER 1922). As already pointed out, position is an important factor in the lethality of air embolism, for more air can be tolerated when the animal is lying on its left side. A further point is that tolerance to intravenously-introduced air is much lower in ill than in normal individuals (SIMPSON 1942). This applies also to decompression sickness (GERBIS and KOENIG 1939; KEAYS 1909; MICHEL 1880; PLESCH 1910).

D. CNS involvement in decompression sickness.

CNS disorders in decompression sickness have been ascribed variously to 1. CNS ischemia resulting from obstruction of the right side of the heart by gas bubbles, 2. CNS ischemia resulting from obstruction of the pulmonary arteriolar tree by gas bubbles, 3. embolization of the CNS by gas bubbles, 4. infarction of the CNS by gas bubbles traversing the spinovertebral system of veins, 5. CNS vasomotor disturbances (arteriolar spasm) occurring as a reaction to circulating tissue products which have entered the circulation following rupture of cells, particularly fat cells, by growing gas bubbles, and 6. formation of gas bubbles within the CNS. The weight given these different pathogenetic factors has varied depending on the nature and rapidity of the decompression, whether to altitude or from increased atmospheric pressure. The factors of obstruction of the right side of the heart and of the pulmonary arteriolar tree have been discussed (pp. 1608—1609).

1. Gas bubble embolization of the brain and meninges.

While it is evident in rapid decompression from *increased atmospheric pressure* that the majority of gas bubble emboli are retained in the lungs, it has long been recognized—since BERT's proposal in 1878—that bubbles may pass through the lungs to be distributed as arterial emboli to the CNS and elsewhere. Gas bubbles have been observed in pial vessels of the spinal cord and brain in autopsied human beings exposed to more than 2 atmospheres (BERT 1878; HELLER et al. 1900; KEAYS 1909; VON SCHRÖTTER 1906; ZOGRAFIDI 1907) and in pial and CNS vessels and occasionally the CSF of experimental animals similarly exposed (BERT 1878; BOYCOTT et al. 1908; CATSARAS 1890; HILL and GREENWOOD 1907; OUDARD 1911), and even in lymphatic vessels (QUINCKE 1910). There has, however, been no way of knowing whether bubbles seen at the time of death had been present at the same place during life. BOYCOTT et al. (1908) have drawn attention to the fact that on cessation of the circulation the blood remains in a supersaturated state for an indefinite period, with the result that bubbles continue to form post mortem. In one rabbit which they exposed to 75 pounds atmospheric pressure and sacrificed and opened up immediately, no bubbles were found, but an hour later a few were seen in the inferior vena cava. Furthermore, they never observed bubbles in the retinal vessels of goats during life, but saw many there post mortem.

The observations by WAGNER (1945) on cats are significant in that the circulating blood in pial vessels was directly visualized through a FORBES window in the skull during decompression from increased atmospheric pressure. When the cats were subjected to an atmospheric pressure of 75 pounds per square inch (gauge pressure) for 1 hour and then decompressed in 3 to 5 seconds, gas bubbles were always seen first in pial arteries, and then, after the circulation in the affected region had slowed, they appeared in adjoining veins.

In cats which died within a *short time* (6 to 80 minutes) after decompression, gas bubbles were seen in pial vessels of only some animals; however, post-mortem studies revealed abundant bubbles in fat, mesenteric vessels, and the right heart. It was believed that under these conditions the bubbles had caused death by reaching vital centers of the CNS without appearing in the pial field under observation. In cats which died a *long time* (3 to 8 hours) after decompression the incidence of bubbles passing through pial vessels was approximately the same. In this group, bubbles were also found in the right heart, in the mesenteric vessels, and in fat tissue. Bubbles were seen in mesenteric vessels as late as 8 hours after decompression. Only minor changes in the caliber of bubble-containing pial vessels was noted.

The explanation offered for the delayed deaths was that collections of bubbles in arteries and veins not essential to life had moved on to vessels in more vulnerable regions, e.g., from gastrointestinal tract to heart, to lungs, and to brain. WAGNER felt that intravascular gas bubbles were formed in all the cats following decompression and that they passed through the heart into the lungs, where one of three events occurred: 1. the gas bubbles were eliminated, 2. they obstructed branches of the pulmonary artery, or 3. they were reduced in size through resorption and then passed through the pulmonary capillaries into the left heart and into the general circulation.

2. The pulmonary filter.

As we have just noted, WAGNER has presented strong evidence in cats that gas bubbles may traverse the pulmonary vascular system and enter the general circulation. HELLER et al. (1900) had reached the same conclusion from observa-

tions in their decompression experiments. In his Thèse de Paris, CASSAIGNE (1934) cited the observations of MAGENDIE and VULPIAN and numerous others to the effect that the rapid introduction of air into systemic veins leads to death principally as the result of cerebral embolization. He noted symptoms of a focal neurological nature in 7 to 12 rabbits (58%) subjected to venous air embolism. KLEINSCHMIDT (1915) found in rabbits that when 1 cc. of air was added to a colored solution injected into the pulmonary artery the colored solution reaching the pulmonary veins and heart contained many bubbles. In BERGSTRAND's (1924) mind there was also no question that a permeable filter existed, for in rabbits he observed bubbles in the circulating carotid blood stream regularly for as long as 25 minutes after air had been injected into systemic veins. LHERMITTE and BARRELET (1934) reached the same conclusion experimentally, and LHERMITTE and CASSAIGNE (1934), on the basis of the development of hemiplegia in man and of neural manifestations in experimental animals following venous air embolism. In the experience of others the incidence of traversal of the pulmonary filter by gas bubbles, based on clinical manifestations in experimental animals, has ranged from 12.5 to 34% (CURTILLET 1939; JACQUET 1937; SINGH 1936; VILLARET and CACHERA 1938).

In mice, guinea pigs and other mammals, including man, SJÖSTRAND (1935) has observed relatively large blood sinuses in alveolar walls, sometimes dilated to form lakes of blood, sometimes not. He has suggested that these sinuses may represent collapsible arteriovenous anastomoses such as are seen in the periphery, which would allow air bubbles to traverse the pulmonary circulation. It is probable that in the rodents at least, these collections of blood are isolated from the general stream in consequence of the sphincteric action of small arterioles. The exact location of this blood, variously stated to be in "sinous" spaces, or "interstitially," is not clear, nor is there any suggestion that these spaces, or channels, represent shunts between the pulmonary artery and pulmonary vein that would allow a more direct transmission of gas emboli. That arteriovenous shunts exist in the *isolated* normal human lung has been demonstrated by TOBIN and ZARAQUIEY (1950, 1953), as follows:

> Shunts between the pulmonary artery and veins were evident from the passage of glass spheres 10 to 500 microns in diameter through the pulmonary artery and into and through the pulmonary veins. An average of 37.5 spheres were recovered from each lung and the fact that they were up to 50 times the accepted size of capillaries indicated that they must have passed from artery to vein by way of shunts of precapillary size. Casts of these vessels, made by injecting them with liquid latex or vinyl acetate, demonstrated that these shunts were located in the lobules of the lung and in the visceral pleura. Anastomoses of precapillary size between bronchial and pulmonary arteries were also found.

3. Cardiac shunt.

In the presence of a probe patency of the atrial septum (observed in 20 to 25% of all individuals [PATTON 1953]) or other septal defect, gas bubbles in the right side of the heart may gain the left side and enter the general circulation. The pressure in the two auricles is approximately the same, and when the pressure in the right side of the heart is increased as a result of tamponading of the lungs with gas bubbles, the bubbles in the right auricle could readily pass into the left auricle. Shock is an additional factor contributing to the relative increase in right ventricular pressure (MARTLAND 1945). Under conditions of increase in right ventricular pressure, it is possible that the blood flow from the right side of the heart may be reversed through arterioluminal and arteriovenous communications (BATSON and BELLET 1930; GOULD 1953).

4. The possibility of the passage of gas bubbles to the CNS by way of the spinovertebral system of veins.

This subject is discussed on pp. 1603, 1625 and 1657. To our knowledge, no factual data on this possible route for the passage of bubbles to the brain are available. WAGNER's observation that in decompression the bubbles reaching the CNS appear first in arteries (p. 1610) seems to be a clear indication that they traversed the lungs. This is not to say that bubbles may not also reach the brain via the spinovertebral system of veins. These veins carry much more blood than ordinarily realized. Retroperitoneal and epidural fat, drained by these veins, are ample N_2 reservoirs. It seems possible that with the individual in the upright position, gas bubbles ascending in this venous system could gain pial veins and the dural sinuses, particularly the superior sagittal sinus, and thus interfere with venous return from the brain. Gas bubbles have been observed in the dural sinuses of rats and guinea pigs decompressed from 4 or 5 atmospheres (following 45 to 160 minutes' exposure) in 5 to 20 seconds (QUINCKE 1910). Infarction of the cortex, such as observed in sinus thrombosis, has not, however, been found in decompression sickness.

5. Arterial air embolism.

In an effort better to interpret the clinical manifestations in decompression sickness, it will be helpful to outline briefly the manifestations of arterial air embolism. The chief hazards are obstruction of the CNS and coronary arterial beds.

BERGSTRAND (1924) laid stress on the *CNS manifestations*, which he ascribed to local CNS ischemia: namely, dyspnea, respiratory spasms, increased blood pressure, blindness, convulsions, and coma. The neurological manifestations listed by DURANT (1935) and DURANT et al. (1947) were aphasia, blindness, hemiplegia, monoplegia, unconsciousness, and convulsions, either generalized or of the Jacksonian type. The occurrence of blindness has been emphasized by NAEGELI (1925). Hemiparesis lasting many months has been reported (VILLANI; cited by DURANT 1935). According to MARTLAND (1945), if death occurs it is usually delayed for a few days. SIMPSON (1942) has described a case of crossed paralysis lasting 18 hours following arterial air embolism, after which the paralysis disappeared. In their studies of dogs in which the pial vessels were directly observed through a FORBES-WOLFF window in the skull, VILLARET and CACHERA (1938) found that as soon as air bubbles appeared in pial arteries (following injection of 5 to 20 cc. of air in the pulmonary vein), the general arterial pressure rose temporarily and that with increasing air in the pial vessels the arterial pressure fell, after which death occurred.

The hazard of *coronary occlusion* in the course of arterial air embolism has been emphasized by MOORE and BRASELTON (1940). They found that when air was introduced into the pulmonary vein, air bubbles appeared consistently in the coronary arteries within a second or two. Directly observing the exposed heart of dogs, DURANT et al. (1947) noticed an ischemic disturbance in the myocardium when as little as 0.025 cc. of air was injected into the anterior descending branch of the left coronary artery. As little as 0.05 cc. sometimes proved fatal. Working on guinea pigs in which bronchovenous fistulae were produced by raising the intratracheal pressure sufficiently to rupture alveoli and their blood vessels, RUKSTINAT and LECOUNT (1928) found that convulsions invariably occurred when the pressure was raised to 30 mm. Hg, and death in 50 to 75 seconds when the pressure was increased to 45 mm. Hg. The coronary vessels in such animals were found to be filled 50 to 90% with air. Myocardial infarction in arterial air embolism has been verified microscopically by LUCAS (1936).

Cerebral air embolism tends to occur when the animal's head is higher than the level of the arch of the aorta, and coronary air embolism when the head is down (DURANT et al. 1947; HAMBY and TERRY 1952; JACQUET 1937; VAN ALLEN et al. 1929). Gravity does not, however, cause air injected intravenously to travel against the blood stream (WOLFFE and ROBERTSON 1935).

6. Tissue trauma from decompression and the problem of shock.

As brought out in the following sections on the clinical manifestations of decompression sickness, shock is a relatively frequent complication of decompression whether to altitude or from increased atmospheric pressure. In airmen, shock may occur at altitude and/or after return to ground level. Some authors

hold that gas bubble embolization of the CNS is responsible under both circumstances, and others that CNS vasospasm, induced by the circulating products of tissue damage, is the responsible factor in both. There are still others who favor CNS bubble embolization as the cause of the shock at altitude, and CNS vasospasm, brought about by the circulating tissue products, as the cause of the delayed shock.

FERRIS et al. (1951) were among those who expressed the view that the shock developing at altitude and after descent may be an expression of a cerebral vasomotor reaction to some product of tissue damage incident to decompression. GERBIS and KOENIG (1939) held much the same view with respect to decompression from increased pressure atmospheres. That fat-containing cells in human subjects may be disrupted during decompression to altitude is strongly suggested by the presence of fat emboli in the lungs post mortem (HAYMAKER and DAVISON 1950). Moreover, in decompression from high atmospheric pressure, necrosis of fat, followed by giant cell reaction and conversion of the fat to calcium soap, may occur (BOYCOTT et al. 1908). Delayed shock in the absence of recognized focal CNS symptoms (Tables 1 and 2; pp. 1614—1616) has been cited as evidence in favor of the tissue trauma theory, but it could be argued with equal conviction that the delayed shock is due to the passage of gas bubbles through the pulmonary filter as a consequence of their reduction in size incident to recompression. CATCHPOLE and GERSH (1946) (p. 1607) have reached the conclusion that since the gas bubbles found in the pulmonary and coronary arteries at altitudes seemed too few to cause asphyxia or heart failure, death probably was due to gas bubble embolization of vital parts of the nervous system. It seems more logical to conclude that since gas bubble emboli were few, death must have been due to some other factor, *e. g.*, traumatic shock. RAIT (1952) suspected that a biochemical disturbance, such as upset of nucleotide metabolism, may serve as a trigger mechanism.

In any search into the etiology of decompression sickness, consideration must be given to the *modifications of peripheral blood flow* which occur during the initial stages of decompression. Prolonged spasm of arterioles of the scleral conjunctiva in the absence of bubbles in the conjunctival vessels has been noted at a simulated 15,000 ft. (4,570 m.) in human subjects who, at the time, had no symptoms of decompression sickness (KNISELY 1943). These subjects also had a prolonged finger-nail-bed refilling time and a prolonged arm vein refilling time. A decrease in digital blood flow has been consistently found at a simulated 38,000 ft. (11,580 m.), again in subjects free from symptoms of decompression sickness (CLARKE et al. 1943). Furthermore, a correlation has been established between the extent of the reduction in the peripheral (digital) blood flow and the average time of appearance of decompression sickness (KAUFMAN et al. 1944). To carry the matter a step further, a relationship has been observed between fall of blood pressure and pulse rate, on the one hand, and bends, chokes, etc. on the other (MAHADY 1943, 1944).

Attacking the problem in dogs, LIPIN and WHITEHORN (1951) observed that at 35,000 ft. (10,670 m.) simulated altitude, no significant alterations occurred in heart rate, stroke volume, cardiac output, or systolic, diastolic, mean or pulse pressures, but skin temperature was lowered by as much as 4.8° F., indicating a reduction in the peripheral blood flow. They reasoned that this alteration could not have been of central origin because of the lack of significant change in the total peripheral resistance, and suggested vasomotor reflexes induced by accumulations of gas in body tissues as the responsible factor. CLARKE et al. (1943) reached much the same conclusion. LIPIN and WHITEHORN concluded by asking:

"Is the reduction of peripheral flow with its inevitable effect on the clearance of nitrogen from the tissue fluids, the primary etiologic agent in the subsequent development of the symptoms of decompression sickness? Or does accumulation of extravascular gas, as suggested above, provide the stimulus for reduced flow, decreased clearance of nitrogen, further accumulation of gas, and the establishment of a vicious cycle which culminates in the subjective evidence of decompression sickness?"

Table 1. *Symptomatology of 12 fatal cas*

All subjects were participating in routine decompression chamber runs except for three who were i
Cases 1—5 were previously reported by HAYMAKER and DAVISON (195

Case No. AFIP No. Age	Obesity	Altitude, Duration of "Flight" feet and meters	Duration of Illness	Onset after Reaching Altitude	Symptomatology during or at end of flight: Bends (B) Chokes (C) Paresthesias (P) Abd. Pains (AP) Nausea (N) Vomiting (V)	Primary Shock	Paresis or Paralysis	Diplop or Strabis mus
1* 95412 25 yr.	Slight (heavily built, musc.)	38,000 (11,580 m.) 72 min.	8½ hr.	1 hr., 5 min.	P, N	2+	—	—
2 103767 22 yr.	Mod. (180 lb., 5′10″)	38,000 (11,580 m.) 75 min.	17 hr.	1¼ hr.	—	1+	—	+
3** 100822 38 yr.	Marked (200 lb.)	30,000 (9,140 m.) 60 min.	17½ hr.	20 min.	B, C, P	2+	Rt. arm	+
4** 127451 23 yr.	Slight (180 lb., 5′10″)	30,000 (9,140 m.) 30 min.	2 days, 7½ hr.	30 min.	C	3+ Semicon-scious	Left leg	+
5** 100893 26 yr.	Slight (184 lb., 6′0″)	38,000 (11,580 m.) 50 min.	3 days, 10 hr.	10 min.	B, C, AP	1+	Rt. hand	—
6 113646 22 yr.	0 (162 lb., 5′8″)	20,000 (9,140 m.) 23 min.	1 day, 15½ hr.	10 min.	C, N	4+ Uncon-scious	—	—
7 293075 33 yr.	Mod. (181 lb., 5′10½″)	40,000 (12,200 m.) 35 min.	1 day, 21 hr.	3 min.	B	4+	Left arm and leg, Rt. face	—
8 Case of SPROULL (1951) 29 yr.	"Obese"	30,000 (9,140 m.) 55 min.	10½ hr.	Immedi-ately	AP	1+ Pale, shaky	—	—
9 Case 3 of COTES (1953) 37 yr.	Mod. (161 lb., 5′4″)	40,000† (12,200 m.) 30 min.	5½ hr.	1 min.	C	1+ Uncon-scious?	—	—
10 Case of STEWART (1954) 28 yr.	0 ("Average wt.")	35,000 (10,670 m.) 2 hr.	17 hr.	1 hr., 50 min.	B, C?	1+	—	
11 570889 50 yr.	Mod. (235 lb., 6′0″)	35,000 (10,670 m.) 90 min.	11½ hr.	1 hr., 10 min.	AP	4+ Uncon-scious	—	
12 638482 34 yr.	Marked (250 lb., 5′11″)	29,000 *** (8,840 m.) 1 hr., 50 min.	6 hr.	1 min.	—	4+ Uncon-scious	Numb-ness left side of body ††	

* Reported also by MASLAND (1943b), and GOGGIO and HOUCK 1945). ** Reported also by MASLA
† At 25,000 ft. (7,520 m.) for ¼ hour, then to 40,000 ft. in rapid ascent, when symptoms began; severe he
heart ceased beating, but patient was revived by artific

decompression sickness (to altitude).

tual flights (Cases 8, 11 and 12). In Cases 11 and 12 a patent foramen ovale was found in the heart. nd Cases 1—6 by ADLER (1950). 0, negative; —, no data.

Latent, or Symptom-Poor, Period	Symptomatology after flight						
	Bends, Chokes, etc.	Secondary Shock	Early Loss of Consciousness	Conjugate Ocular Paralysis (P) Vert. Nystagmus (N)	Paresis or Paralysis	Positive Babinski Sign	Convulsions
1 hr.	C, N, V	*Fulminating*	0				—
50 min.	AP, N, V	Slowly progressive	0	—	—	—	—
15 min.	N, V	Mod. progressive	0	—	—	—	—
0	V	Fulminating§	+	—	Left leg, then arm	Left	+
45 min.	V	Mod. progressive	+	+ (P) + (N)	Rt. hand, then leg	Bilateral	+ §§
0	—	Delayed, then progressive	0	—	Rt. face	Bilateral	+ §§
0	—	Delayed, then progressive	+	+ (P)	Left arm and leg, Rt. face	Bilateral	—
0	AP, N, V	Rapidly progressive	0	0	0	0	—
30 min.	N	Delayed, then progressive	0	+ (P)	—	Plantar reflexes absent	—
2 hr., 15 min.	C, V	Delayed, then progressive	0	—	—	—	—
0	—	Fulminating	+	—	—	Bilateral	+
0	—	Fulminating	+	—	Left side of body	0	—

(1943b, 1946, 1948). *** Flight was at 39,500 ft. (12,040 m.), but jet cabin was pressurized to 29,000 ft. ache was a feature of the post-flight course. †† This patient also had opisthotonos. § At end of 3d hour, respiration. §§ These patients also had nuchal rigidity and trismus.

Table 2. *Clinical, laboratory and post-mortem data related to the development of shock.*
The numbering of the cases is the same as in table 1. N, neutrophils; L, lymphocytes; Post M, post mortem; RBC, red blood cells; WBC, white blood cells.

Case No.	Duration of Illness	Blood pressures (at times after onset)	Signs of pulm. edema	Laboratory data						Post-mortem data			
										Lungs		Fluids	
				Time test done	RBC (million)	Hb (%)	Hematocrit (normal: 45 vol. %)	WBC	Urine	Wt. (Gm.)	Edema	Pleural	Pericard. (cc.)
1	8½ hr.	90/60 (5 min.) ?/? (1 hr., 10 min.)	+	—	—	—	—	—	—	907	+	1300 cc. SG 1.002 Protein 4.4 Gm. % RBC 500/cmm. WBC 27/cmm.	150
2	17 hr.	66/? (7 hr.) 60/? (12 hr.)	—	—	—	—	—	—	—	—	+	1200 cc.	5
3	17½ hr.	140/100 (1 hr.) 120/80 (5 hr.) 90/? (6 hr.)	+	2½ hr.	5.4	90	60	23,000 (N90, L10)	—	1592	+	1500 cc. SG 1.020 Protein 6.9 Gm. % WBC 21/cmm.	10
4	2 days, 7½ hr.	120/80 (40 min.) 102/80 (3 hr.)	+	17 hr. 20—35 hr.	5.8	110	57 53, 51, 47, 47	20,000 (N92, L8)	—	1785	+	60 cc.	20
5*	3 days, 10 hr.	100/60 (5 min.) 110/76 (1 hr.) ?/? (17 hr.) 122/90 (24 hr.)	+	1½ hr. 4½ hr. 5½ hr. 6½ hr. 48 hr.	— — — — 4.2	— — — — 85	55 56.1 60 64 —	— 20,200 — — 13,500 (N87, L13)	— — — — Alb. 4+ SG 1.017	—	+	0	30
6†	1 day, 15½ hr.	137/80 (30 min.) 135/90 (3 hr.) ?/? (6 hr. ?) ?/? (7 hr. ?) 136/92 (8 hr.)	+	—	6.2 5.1 5.7 5.4	124 100 110 103 121 118	55, 51, 57, 47 49, 47, 52	29,850 (N95, L5)	—	1700	+	0	75

7	1 day, 21 hr.	135/80 (2 hr.) 126/90 (7½ hr.) 118/52 (18 hr.)	0	—	—	—	10,800 (N 68, L 30)	Alb. 4++ Casts 1+ RBC 1+	1000	+	—	35	
8	10½ hr.	?/? (2¼ hr.)	0	+	—	—	—	—	—	+	500 cc.	50	
9	5½ hr.	140/100 (20 min.) 125/83 (1 hr.) 110/? (2½ hr.)	+	1 hr. 3½ hr. 4 hr.**	65 69	130 135 146	— — 17,000	(Post M) Alb. 1++ Casts 1++ RBC 1+	1010	+	730 cc.	11	
10	17 hr.	?/? — ?/? —	+	—	—	—	—	—	—	+	1100 cc.	—	
11	11½ hr.	190/100 (15 min.) 70/45 (30 min.) 106/60 (45 min.) 90/50 (1 hr.) 130/? (6 hr.)	—	—	—	—	—	—	1375	+	100 cc.	—	
12††	6 hr.	180/120 (30 min.) 130/90 (50 min.) ?/? (6½ hr.)	0	—	—	—	—	—	1000	+	0	0	

* About 5 hours after decompression a gas bubble was noted in the middle ear. ** 1 pint of physiological saline had been given intravenously.
† CO_2 capacity 52, 31, 50, 50 vol.%; sedimentation rate 14, 10, 2, 28, 39, 47, 24; S.G of whole blood 1.063 and 1.066 (normal); S.G. of plasma 1.028 and 1.025 (normal); bleeding times 2 min. 20 sec., and 3 min. 45 sec.; clotting times, 3 min., and 4 min. 15 sec.
†† About 1 hour after onset the spinal fluid was clear and under 112 mm. H_2O pressure.

E. The spinal cord as a site of predilection of involvement in decompression sickness.

The paraplegia of spinal origin occurring in experimental animals and human beings decompressed from high pressure atmospheres is usually ushered in by respiratory embarrassment, but may occur unexpectedly without premonitory symptoms. BEHNKE and SHAW (1937) have readily induced paraplegia in animals by quickly decompressing them from increased pressure atmospheres and then partially recompressing them to a degree which prevented death by asphyxia. On the other hand, it is exceptional for paraplegia to occur as a result of decompression to altitude. In TROWELL's (1941 a & b) experience neither clinical nor histological evidence of spinal cord involvement was observed in animals which had been rapidly decompressed to 40,000 or 47,000 ft. (12,200 or 14,300 m.), while in SMITH's (1942), paraplegia developed in only 1 of many dogs thus exposed. In human cases of decompression to altitude, paraplegia is also uncommon (p. 1644).

Numerous views as to the pathogenesis of the lesions in the spinal cord have been expressed.

DRASCHE (1898), LEYDEN (1878), NIKIFOROFF (1893) and NORDMANN (1928) were of the opinion that the rapid expansion of intravascular gas (chiefly CO_2) during decompression exerted a kind of explosive action which ripped the cord substance. HELLER et al. (1900) and VON SCHROETTER (1904) argued that the volume of gas released through decompression

was relatively too small to have such an effect, but thought it possible that large quantities of gas bubbles in vessels might mechanically exert undue pressure on neural elements and have a shearing action on the neural meshwork. HOCHE's (1897) view that gas bubbles have an embolic action exactly like that of solid substances has been discredited many times over by the observation that embolization by solid substances involves grey matter as well as white and is always irreversible. It is of some historical interest that selective loss of temperature sensibility has been ascribed to collection of gas in the central canal of the spinal cord (QUINCKE 1910).

In decompression sickness, the basic disturbance in the spinal cord is that of ischemia, which frequently is limited to the white matter. The mode of development of the ischemia is, therefore, the problem that confronts us. An important phase of this problem is the predilection for involvement of the thoracic segments. The causative factors to be considered include 1. gas bubble embolization of the cord, 2. autochthonous gas bubble formation in myelin sheaths and N_2 clearance, 3. capillary richness of the cord, 4. arterial supply of the cord, and 5. venous return from the cord.

1. Gas bubble embolization.

In a reduction of blood flow to the entire spinal cord produced by ligation or compression of the abdominal or thoracic aorta, the grey matter bears the brunt of the insult; the richness of collateral blood supply through the arteriae coronae is such that the obstruction must persist 20 to 45 minutes or longer before irreversible ischemic changes occur (RIGHETTI 1899; KROGH 1945, 1950). Both the grey and the white matter are also involved as a consequence of sudden reduction of blood flow through the intercostal arteries in dissecting aortic aneurysm (REITTER 1916). Moreover, the cervical spinal cord is exceedingly resistant to ischemia induced by obstruction of the carotid blood flow to the CNS (GRENELL 1946). Since the selective involvement of the white matter occurring in decompression sickness cannot be ascribed to generalized spinal cord ischemia or hypoxia (from pulmonary asphyxia, for example), the only conclusion to be reached is that the white matter involvement is due, primarily at least, to focal gas-bubble-induced ischemia. Degree of compression and rapidity of decompression are among the etiological factors influencing the development of the embolization, as is evident from CATSARAS's (1890) observations on 3 dogs, as follows:

One dog immersed to a simulated 23 fathoms (42 m.) for $1^1/_2$ hours and then decompressed in 1 minute showed no untoward symptoms, and $6^1/_2$ hours later was sacrificed. With the aid of the hand lens small bubbles were seen in many blood vessels of the cord. In a *second dog*, exposed to a simulated depth of 25 fathoms (46 m.) for an hour, then decompressed over a period of 50 seconds, paralysis of the hind limbs appeared in 13 minutes, and during the ensuing 20 minutes the paralysis disappeared. Some 20 minutes later the animal was sacrificed. Sectioning of the cord disclosed bubbles only in segments of the lumbar enlargement, mainly within vessels. In the *third dog*, taken to a simulated 28 fathoms depth (51 m.) for $^1/_2$ hour and decompressed in 40 seconds, paralysis of the hind legs was noted at the end of about 13 minutes. The paralysis persisted until the following day, when the animal was sacrificed. The lumbar enlargement of the spinal cord showed advanced softening. Bubbles were seen in the middle of the softened area, but nowhere else.

2. The question of autochthonous bubble formation.

Since gas bubble embolization of the spinal cord may occur in the apparent absence of embolization of the brain, bubble population in the CNS circulation cannot be the only factor concerned. While conceding that the lodgment of circulating gas bubbles in vessels of the spinal cord is highly significant in producing local spinal cord ischemia, BERT (1878) and LEYDEN (1878) contended

that an added and important factor is the development of gas bubbles in the parenchyma. The same opinion was expressed by QUINCKE (1910). An example of "autochthonous" bubble formation provided by BOYCOTT et al. (1908) is illustrated in Fig. 4. Although in their animals the bubbles were distributed widely in the cord, areas of softening were usually confined to the white matter of the lower thoracic and upper lumbar segments. GERSH and CATCHPOLE (1951) looked for bubbles in frozen-dried preparations of the cord and found them only within vessels.

BOYCOTT et al. (1908) contended that bubbles are apt to form in white matter because of its "fatty nature." In this connection, BRANTE (1949) demonstrated

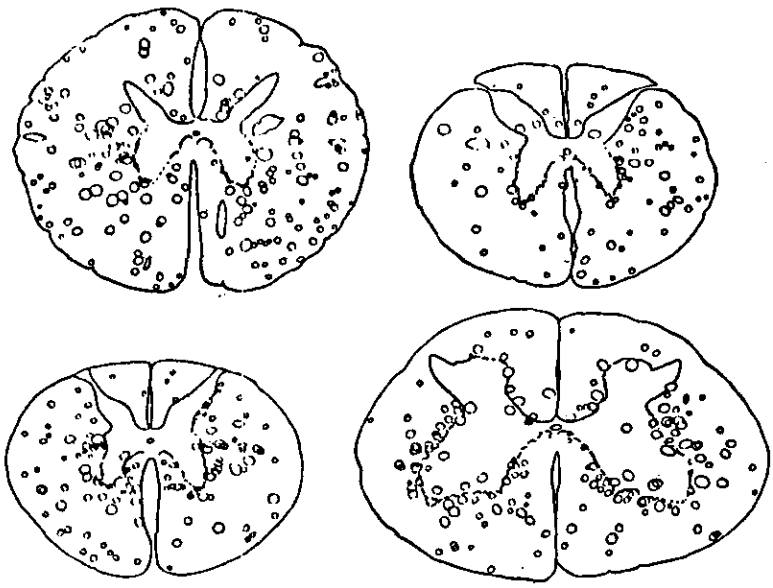

Fig. 4. Distribution of "extravascular" bubbles in 4 regions of the spinal cord of a goat. Each region shows a composite of all the bubbles in a 0.4 mm. length of cord. The animal died shortly after the beginning of a stepwise 2 hour-13 minute decompression after having been exposed for 3 hours at 81 pounds in an atmosphere containing 36% O_2. The bubbles, virtually confined to the white matter, are concentrated in the boundary zone of the grey matter, where the circulation is least efficient. (Lesions restricted to this region are to be seen in Fig. 10 B) (From BOYCOTT et al. 1909.)

that the white matter of the cord is definitely richer in lipids than that of the cerebrum, for the reason that the fibers have a higher myelin-sheath-volume/axis-cylinder-volume ratio. Thus, from this standpoint the spinal white matter would be more subject to autochthonous bubble formation than the cerebral white matter.

BRANTE (1949) also found that *spinal roots* have a higher lipid content per unit of tissue than the white matter of the spinal cord. This quantitative difference in spinal cord and spinal root lipids might serve as an explanation of the observation by GERSH and CATCHPOLE (1951) on frozen-dried CNS tissues of compressed-decompressed animals, that the myelin of peripheral nerves contained numerous gas bubbles (Fig. 3C), while that of the spinal cord was bubble-free. The SCHWANN sheath would not interfere with gas diffusion from nerve fibers but might hinder the escape of gas bubbles from the SCHWANN tubule and thus, mechanically at least, be prejudicial to the normal functioning of nerve fibers.

A possible key to the problem of autochthonous bubble formation is the degree of *uptake of inert gas by the spinal cord*. The only data available are those of KETY et al. (1954). These workers succeeded in measuring in cats the circulation in the grey and white matter of the cervical cord by the use of the relatively

inert gas, trifluoro-iodo-methane, which is approximately 40 times more soluble in body tissues than N_2. The method, outlined in part by KETY et al. (1953), consists of administering isotope-tagged gas to an animal until the saturation point is reached, removing the animal's head and quickly freezing it in liquid air, sectioning the frozen head and neck, and measuring the radioactivity of the various structures of the brain and cervical cord by means of autoradiography. They stated that "the concentration of that gas in any tissue after a definite time interval is a function of its concentration in the arterial blood during that time, and of the capillary blood flow, diffusion and solubility of the gas in the tissue." In brief, KETY et al. (1954) noted that the concentration of gas was roughly twice as rich in CNS cortex as in the white matter, and quantitatively was of much higher concentration in the brain than in the spinal cord. Considering cerebral cortex, cerebral white matter, spinal cord grey matter, and spinal white matter, the ratio of gas concentration, hence vascular density, was approximately 50:18:25:10. These data, indicating that the vascular density of the spinal white matter is much less than that of the cerebral white matter, provide the key to the selective involvement of the cord by gas bubbles circulating freely in the CNS. They also indicate that the saturation-desaturation time of N_2 is longer in the spinal cord than in the cerebrum. This would mean that with saturation of the cord by N_2 during compression, there would be a greater tendency for autochthonous bubble formation to occur in the cord than in the brain during decompression.

Whether autochthonous bubble formation does actually occur under conditions of rapid decompression from prolonged compression is still a moot point. Paraplegia has been observed in experimental animals subjected to air embolism (CASSAIGNE 1934; VAN ALLEN et al. 1929), and if this signifies spinal cord involvement—as presumably it does—then the spinal cord may be affected by circulating gas bubbles without the benefit of autochthonous bubble formation. In the presence of disturbances of capillary circulation the N_2 supersaturation both of tissues and of slowly flowing or stationary capillary blood remains high, i.e., the supersaturation coefficient increases as the hemostatic pressure decreases. It may well be that a slowing of circulation in the spinal cord as the consequence of gas bubble embolization is propitious for autochthonous bubble formation, causing, as PFLEIDERER (cited by HORNBERGER 1950) phrased it, "gas thrombosis" in addition to gas bubble embolism.

3. Vascularity as a factor in the vulnerability of the spinal cord in decompression sickness.

HELLER et al. (1900) recognized that only when the volume of gas bubbles in vessels relative to the richness of the circulatory bed is too great, is there a sufficient reduction in blood flow and intravascular pressure to bring the gas bubbles to a halt, thus allowing them to act as emboli. In considering the peculiar vulnerability of the thoracic segments of the cord from the vascular standpoint, two factors come into consideration: 1. capillary density, and 2. arterial supply.

1. All reports agree that *capillary density* is greater in the grey matter than in the white. STERZI (1904) noted in vertebrates that from the lowest classes to the mammals the vascularity of the grey matter increases both relatively and absolutely as compared to the white matter. The greater capillary density of the grey matter has been ascribed not to the number or mass of nerve cell bodies but to the richness of synaptic connections, i.e., the density of neuropil (DUNNING and WOLFF 1937). The literature seems devoid of data on the capillary density of the spinal cord at different levels. From KADJI (1889) we learn, however, that in cross sections of the cord of man the capillary beds of the three columns of white matter

are of equal density, which is in contradiction of KRAUSE's (1876) statement that the density differs, the capillary mesh being narrowest (i.e., richest) in the posterior columns (particularly the fasciculi graciles), widest in the anterior columns, and of intermediate width in the lateral columns. According to KOELLIKER (1896), the finest capillaries in the spinal cord of man are 5 microns in diameter, those of the brain 4.5 microns—and of the capillaries in the cord those in the white matter have a somewhat greater diameter. In a study of the capillary richness of the third cervical segment of the spinal cord of albino rats, CRAIGIE (1920) noted that the capillary bed had the following order of increasing richness: fasciculus cuneatus, ventral column, lateral column, pyramidal tract, with the pyramidal tract about twice as richly supplied as the fasciculus cuneatus. A subsequent study of albino and wild rats (CRAIGIE 1931, 1933, 1938) disclosed that the average capillary length in the pyramidal tract is twice that of the funiculus cuneatus.

With respect to the *capillary density of the anterior horn*, KNOCH (1950) observed in rabbits and in a monkey that capillary density was equal throughout the anterior horn, but that arteries divided into capillaries mainly near the periphery of the horn, while the veins formed mainly at the center. The peripheral nerve cells were thus situated near the arterial ends of capillaries, and the central cells near the venous ends. Inherent in this pattern is the tendency in ischemia of the cord, for the periphery of the horn (which innervates antigravity muscles) to be spared, and the central part (which innervates gravity muscles) to be affected.

2. In considering the *arterial supply of the spinal cord* in relation to the selective involvement of the thoracic segments in decompression sickness, MOXON (1881) and HELLER et al. (1900) suggested that the sparing of the cervical segments in the great majority of cases is contingent on the relative richness of their supply by the vertebral artery. Through its anterior and posterior radicular branches, the vertebral artery supplies *all* cervical segments and the upper thoracic segments. The largest radicular arteries in this region are at C 6. According to BOLTON (1939), the vertebral artery supplies the cervical segments and thoracic segment 1, and according to TUREEN (1938) segment Th 2 as well in some cases. Clinical as well as pathological evidence favors the view that the vertebral artery irrigates all segments down to and including Th 4 (BARTSCH 1954; ZÜLCH 1954).

As to the arterial supply of the remainder of the cord, the *anterior radicular arteries* for the supply of the thoracic segments are much smaller than those supplying the other segments (ADAMKIEWICZ 1882; KADJI 1889; TANON 1908) and the posterior radicular arteries, though of uniform size and always slender, are often missing at levels C 8 through Th 4 (TUREEN 1938). According to KADJI (1889), the largest anterior radicular artery is at a lower thoracic or upper lumbar level (usually Th 10 or Th 11). This vessel, usually referred to as the "artery of ADAMKIEWICZ" (1882), is readily visible in Fig. 5. This photograph illustrates the relative poorness of the arterial supply of the mid-region of the thoracic cord. SUH and ALEXANDER (1939) observed 1 or 2 large anterior radicular arteries in the lumbar region, 1 in the lower thoracic region, 1 or 2 in the lower cervical region, 1 in the upper cervical region, and rarely 1 in the midthoracic region. The largest artery was usually at L 2. These observations would indicate

Fig. 5. Roentgen photograph of the spinal cord in the dural sac, in the newborn human. The arteries were injected with cinnabar. Note that the characteristic segmental arteries have a radicular distribution. The spinal cord is supplied only by 4 or 5 segmental arteries. The poorest arterial supply is in the thoracic region. (Prepared by Dr. OSCAR V. BATSON and Dr. LOIS A. GILLILAN, Anatomy, Graduate School of Medicine, Univ. Penna.)

that much of the blood supply in the thoracic region of the cord is contingent on the arteries of roots C 6, Th 10 or 11, and L 2.

On measuring the diameter of the *anterior spinal artery* of man at various levels, SUH and ALEXANDER (1939) found that this vessel was narrowest at midthoracic levels. Moreover, at any given level the part of the anterior spinal artery halfway between two adjoining significant radicular arteries was relatively the narrowest, making it appear that the region equidistant from large radicular arteries is a watershed between the two adjoining regions of irrigation. This was particularly striking in the mid-thoracic region, where the distance between significant radicular arteries was longest.

In his description of the vascularization of the spinal cord, TUREEN (1938) pointed to three primary arterial chains in the pia (2 posterior and 1 anterior) which give rise, in turn,

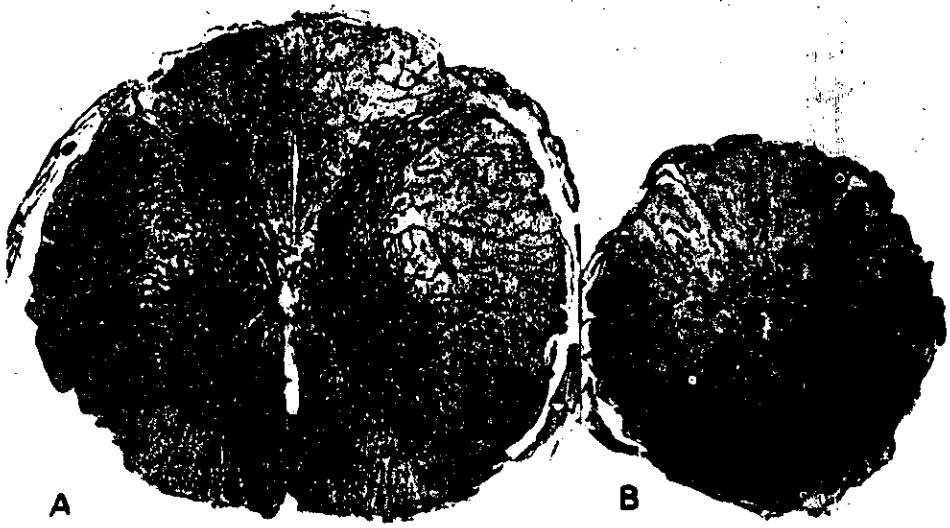

Fig. 6A and B. Vascularization of thoracic and lumbar levels of the spinal cord of the macaque. Both sections are cut at the same thickness. A, lumbar cord; B, thoracic cord. Both × 16. Capillary diameter and density in the white matter of the 2 sections is practically the same. The outstanding difference in the white matter is the paucity of larger vessels in the thoracic cord. (From Section 1-M-26; through courtesy of Dr. KNOX FINLEY, Stanford Univ., San Francisco.)

to secondary chains and ultimately to an arterial network which envelops the cord in large and small meshes (the *arteriae coronae*). These anastomotic pial vessels provide for an even distribution of the blood stream to various parts of the spinal cord, an arrangement necessary because, apparently, the size and location of the radicular arteries do not correspond to the functional needs of the cord. Granting that arteriae coronae tend to equalize blood flow to various segments of the cord, the fact nonetheless remains that the arteriae coronae of the thoracic segments receive less radicular arterial blood than those of the other spinal segments and, therefore, may have less blood readily available to meet exigencies. It is well recognized that the thoracicolumbar part of the cord (thoracic and upper lumbar) is most prone to involvement by thrombosis of the anterior spinal artery, an observation explicable on the basis of relative inadequacy of the collateral circulation in this region. The richest vascular anastomoses of the entire cord are said to be in the lumbosacral region, and considered in its longitudinal extent, the column having the least adequate collateral circulation is the lateral (TUREEN 1938).

A clue to the *predilection of involvement of the central part of the white matter* in decompression sickness is to be found in the pattern of distribution of the anterior and posterior spinal arteries. Some branches from the anterior artery supply the central part of the lateral and anterior columns (HERREN and ALEXANDER 1939; HOCHE 1899; REITTER 1916; TUREEN 1938) and others the central part of the posterior columns (MAIR and DRUCKMAN 1953). KADJI (1889) found that the posterior columns in man are unique in that the most slender branches of the posterior spinal arteries penetrating from the cord's surface have the longest vertical ramification and that at thoracic levels the arterial caliber is smaller than at other levels, and HERREN and ALEXANDER (1939) noted that the longest penetrating

arteries of the posterior columns are laterally situated. It is possible that the relatively long course of the branches of these arteries—called end-arteries (KADJI 1889; TUREEN 1938)—is a factor of importance in the vulnerability of the central white matter. As may be expected in gas bubble embolization of the cord, the ischemic foci in the white matter are often wedge-shaped. Where the embolization is more massive, leading to confluence of foci and loss of tissue, the wedge pattern usually vanishes.

Since the radicular arteries of the thoracic cord are, in general, much smaller than those of other levels, it might be expected that there would be fewer conspicuous *arterioles within the substance of the spinal cord* at thoracic than at the other levels. Examination of the vascular bed of the spinal cord of the macaque proves this to be the case (Fig. 6). On the other hand, the periphery of the cord, usually spared in decompression ischemia of the cord, is supplied by the arteriae coronae.

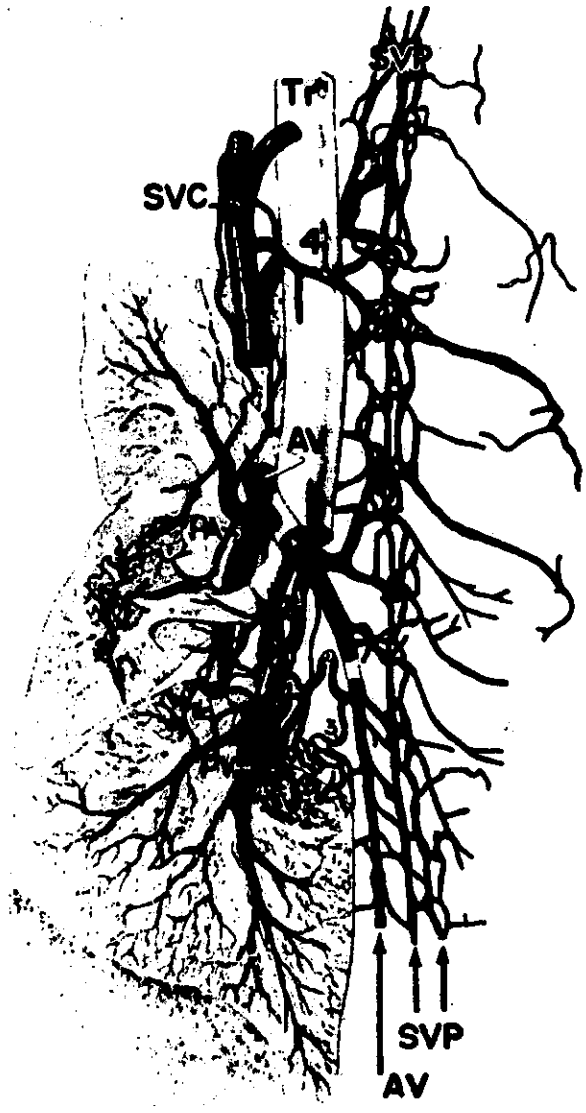

Fig. 7. Drawing of a cast of the right lung and thoracic vessels of a dog, 3 months after ligature of the right pulmonary veins. The medial aspect of the lung is portrayed. Details of the connections between pulmonary, azygos and spinovertebral venous systems are emphasized. The severed ends of the pulmonary artery (*PA*) and azygos vein (*AV*) are visible. There is great expansion of bronchial veins (*1, 2 & 3*) terminating in the azygos vein (*AV*). One vessel (*4*) is seen extending from the superior vena cava (*SVC*) to the spinovertebral venous plexus (*SVP*), and a still patent pulmonary vein (*PV*) connects with an expanded bronchial venous plexus. (From HURWITZ et al. 1954; courtesy of Dr. A. A. LIEBOW, Yale Univ., New Haven, Conn.)

In *summary and conclusion*, then, it is evident that the thoracic segments of the spinal cord have the poorest arterial and arteriolar supply. Through their anastomotic connections the arteriae coronae serve to compensate for this relative deficiency, but the capacity of the arteriae in this direction is obviously insufficient to prevent local ischemia in the face of a large intravascular bubble population. The only adequate radicular arteries are those of segments C 6, Th 10 and L 2, and on the basis of these data ZÜLCH (1954) has concluded that the poorest circulation is in the segments lying at the boundary zones between each two of these apposing arterial supplies, namely at Th 4 and L 1. These conclusions are presumably applicable to spinal cord involvement in decompression sickness.

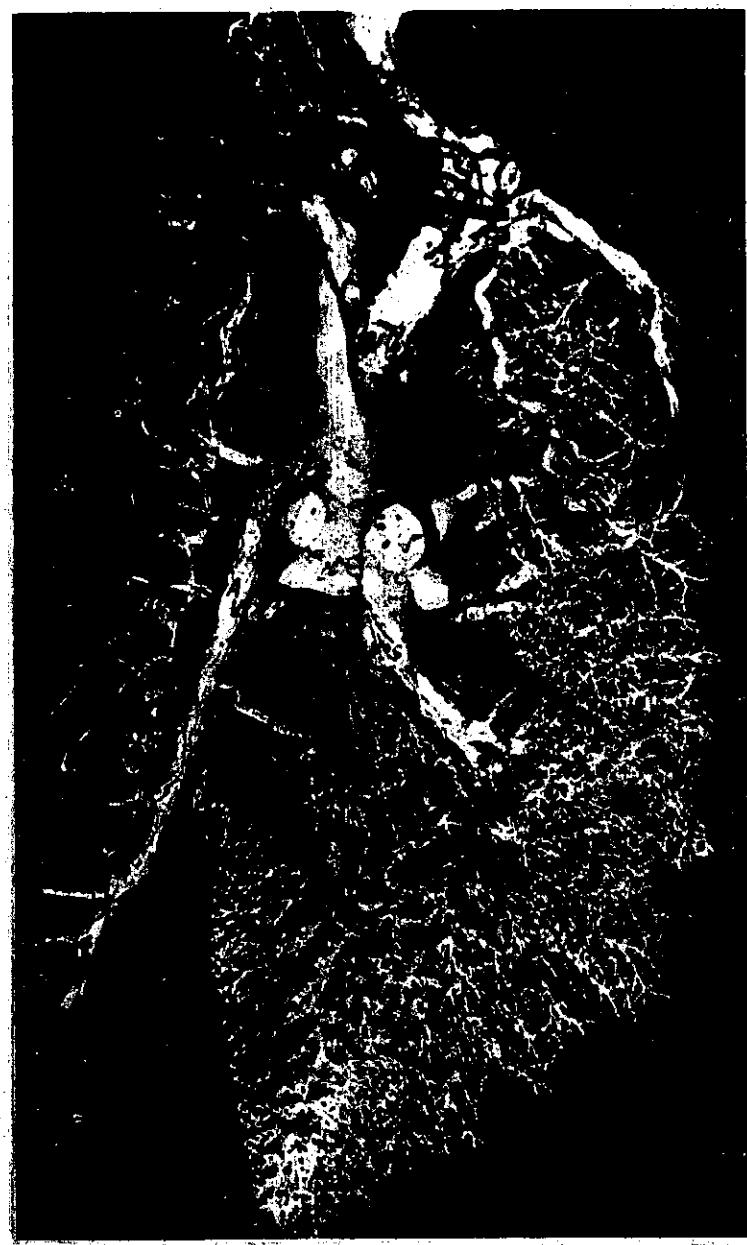

FIG. 8. Medial aspect of left lung of a dog, 4 months after ligature of the left pulmonary veins. The hilar bronchial collaterals (*1, 2 and 3*), draining the lower lobe, extend into the azygos vein (*AV*). The vessels connecting the spinovertebral venous plexus (*SVP*) with the azygos veins are apparent. The upper lobe is drained by large transpleural vessels (*4, 5 and 6*) from the internal mammary vein. (From HURWITZ et al. 1954; courtesy of Dr. A. A. LILLEHEI, Yale Univ., New Haven, Conn.)

4. Retardation of venous return from the spinal cord.

The severity of involvement of the spinal cord in decompression sickness differs considerably from case to case. In some instances there are multiple focal perivascular or wedge-shaped areas of ischemic necrosis (Figs. 9 and 10; pp. 1633 and 1635) which may be considered due to local bubble embolization. In others, much of the white matter of affected segments of the cord is massively

necrotic or has disappeared, leaving a cavity (Figs. 10A and 15, pp. 1635 and 1641). Under the latter condition the lesions may be contingent either on a greater mass of bubbles delivered to the spinal cord or on retardation of venous flow, or both. The occurrence of massive hemorrhage epidurally (pp. 1637—1638) also suggests retardation of venous blood flow as a factor in bubble formation in the spinal cord.

The mechanism through which blood flow in the spinovertebral and epidural veins might be retarded is conjectural. It is possible that gas bubbles developing in epidural fat cells may sufficiently enlarge the epidural fat masses to compress the epidural capillary-venous system and thus retard venous flow from the spinal radicular veins. Another possibility is that blood flow in the epidural and spinovertebral veins is embarrassed by alterations in intrathoracic pressure. Such alterations may in themselves lead to spinal cord damage, for paraplegia has been observed as a complication of longstanding severe asthma (HADDON 1954). BATSON (1940) has pointed out that the blood pressure in these veins is "very low," which would favor the development of bubbles intravenously. The veins being valveless, the direction of blood flow in them is altered with every compression of the trunk, as in straining, lifting, coughing, and holding the breath. HAMILTON et al. (1936) held much the same view. From these considerations it seems possible that gas emboli originating from epidural fat depots could, under such conditions, be propelled into the veins leading into the spinal cord, retarding circulation so as to favor hyperemia, and thus add to the embarrassment of the circulation caused by arterial gas emboli. Retroperitoneal fat might also serve as the source of bubbles reaching the spinovertebral system of veins. Such a mechanism in the production of spinal cord ischemia could serve as an explanation of spinal cord involvement in decompression sickness in the absence of recognizable clinical manifestations of cardiac and pulmonary embarrassment.

A reversal of blood flow in the azygos vein is another means by which venous drainage from the spinal cord might be embarrassed, and thus contribute, through the production of hyperemia, to ischemic infarction of the spinal cord. That blood may actually pass from the superior vena cava into the azygos vein as a consequence of right heart failure has been suggested by FRANKLIN (1937) on the basis of the cinematographic studies of blood flow in the cat and rabbit. Bubbles in the azygos vein were looked for by RUDGE (p. 1629) in a case of decompression sickness in man, but none was found.

BATSON (1940, 1942) has emphasized that the entire system of epidural and vertebral veins has, through the azygos system, a free and rich anastomosis with the veins of the thoracic and abdominal cavities and that direct venous communications exist between the lungs and the spinovertebral and azygos systems. Free communications exist between these systems and the posterior bronchial and parietal pleural veins. In dogs, anastomotic veins extend from the lower lobe of the lungs to upper thoracic levels of the azygos veins, an observation particularly well illustrated by their enlargement after occlusion of the pulmonary veins (Figs. 7 and 8) (HURWITZ et al. 1954). When gas bubbles clog the pulmonary arterial tree, alterations of blood flow in these veins may further embarrass blood flow in the spinovertebral venous plexus.

In *summary*, one may speculate that the paraplegia occurring in the absence of premonitory symptoms of pulmonary and cardiac distress, may be due to arteriolar gas bubble embolization of the spinal cord *plus* embarrassment of spinovertebral venous circulation by gas bubbles arising in epidural and/or retroperitoneal fat. The same would apply to the paraplegia ushered in by symptoms of pulmonary asphyxia except that here the alterations of intrathoracic pressure may be an added contributing factor.

II. Clinical and pathological manifestations of decompression from high pressure atmospheres.

The symptomatology of decompression from high pressure atmospheres may be subdivided into primary and secondary decompression phenomena, an ensemble which led CATSARAS (1890) to refer to the maladies of the maimed sponge fisherman on the Islands of Hydra and Aegina as "une véritable iliade de maux." The primary phenomena are discussed on pages 1658 to 1660. Secondary decompression phenomena, with which the following pages deal, are those due to formation of N_2 bubbles in the tissues and blood stream and their lodgement in the lungs, CNS and elsewhere as a result of too rapid ascent. The major manifestations are 1. bends (pains about the joints), 2. chokes (burning or suffocating sensation in the respiratory passages on inspiration), and 3. paralysis from spinal cord involvement.

A. Signs and symptoms.

1. Incidence.

Decompression sickness has been recorded in somewhat more than 7,000 cases. The incidence of the manifestations varies greatly with the reports of different authors, but is roughly as follows: bends 70—92%, chokes 1.6—6%, auditory and vestibular disturbances 6—10%, asphyxia associated with shock 1.3—4%, unconsciousness 0.5—1%, visual disturbances 5%, aphasia 0.3—1%, diplopia or strabismus 1.3%, hemiplegia 0.1—0.3%, and manifestations of spinal cord involvement 0.6—21% (BASSOE 1911, 1913, BEHNKE 1951; CATSARAS 1890; ERDMAN 1913; GERBIS and KOENIG 1939; HELLER et al. 1900; KEAYS 1909; LEVY 1922; THORNE 1941).

2. Time of onset.

As remarked by POL and WATELLE (1854) of the miners working under compressed air, "on ne paye qu'en sortant." The signs and symptoms usually appear soon after decompression. In the 280 cases reported by LEVY (1922) they developed within the *first hour* in 64.2%, *second hour* 17.7%, *third hour* 6.9%, *fourth hour* 3.2%, and *fifth to eighteenth hour* 7.6%. In THORNE's (1941) series of 300 cases the times of onset were as follows: *first hour* 60%, *second hour* 35%, *third hour* 3%, and *after the twelfth hour* 2%.

3. Manifestations of spinal cord involvement.

The manifestations of spinal cord involvement, which may occur without warning or be preceded by a sensation of oppression in the chest or by girdle pains, may be subdivided as follows:

a) *Predominant lateral column involvement*, most frequent, characterized by paraplegia which is usually accompanied by severe pains, numbness, paresthesias or anesthesia, and occasionally by dissociated anesthesia (BOINET 1906; CAZAMIAN 1912; CATSARAS 1890; GAL 1872; VON HALLERSTEIN 1889; HOCHE 1897) or by quadriplegia or monoplegia with or without sensory changes (BOINET 1906; CATSARAS 1890; MCCALLUM and WALDER 1953; SHARPLES 1894). Monoplegia of a pattern closely resembling that of ERB's palsy has been observed (CATSARAS 1890).

b) *Combined lateral and posterior column involvement*, fairly common, characterized by manifestations similar to those just mentioned plus ataxia and loss of deep sensibility (CATSARAS 1890; MCCALLUM and WALDER 1953).

c) *Predominant posterior column involvement*, least common, characterized by ataxia and loss of deep sensibility (CHARPENTIER 1883; CATSARAS 1890; KLIENEBERGER 1907).

In all three types, *loss of bladder and rectal sphincteric control* is the rule, but like the limb pareses the loss is usually transitory. *Disturbances of genital function*, such as impotence, faulty erection, premature ejaculation and priapism, are also characteristic. *Diaphragmatic paralysis*, usually rapidly evanescent, has been observed. *Muscle atrophy* is uncommon. *Motor irritative phenomena*, including fibrillary and clonic muscular contractions and tremor, are common and are particularly apt to occur in the upper arm, thigh and gluteal region (DOMÍNGUEZ 1912; GERBIS and KOENIG 1939; HELLER et al. 1900; LIE 1904; SILBERSTERN 1895). The spine is often tender, and the trunk and neck stiff. Opisthotonos may even occur (BAUER 1870).

CATSARAS (1890) dealt with many facets of decompression sickness in his analysis of the disabilities suffered by 26 sponge fishermen following dives to a depth of 7 to 34 fathoms (13 to 58 m.), with return to the surface within one minute. The symptoms, which appeared in a few seconds to $10^1/_2$ hours after surfacing, indicated involvement of the lateral columns in 17 (13 bilateral and 4 unilateral), the lateral and posterior columns in 6, and the posterior columns in 8 (with transitory associated lateral column involvement in all 3). Motor disability in the lower limbs ranged from weakness with difficulty in urination to total paraplegia associated with complete anesthesia and abeyance of sphincteric function; in 5 cases of this kind there was transitory paresis of an upper limb. Tremor in affected limbs was common. Loss of position sense, positive ROMBERG test, and crises of pain characterized all those cases in which the posterior columns were involved. Superficial sensibility was lost in the paretic regions in virtually all cases, but was restored in due time. Respiratory difficulty was noted at the onset in 10 of the 26 cases and cerebral symptoms (loss of consciousness, motor aphasia, and blindness, in that order of frequency) in 14, not lasting more than 24 hours except in one case in which unconsciousness persisted for 3 weeks.

In 36 other cases the clinical manifestations included asphasias, transitory mania, epileptiform seizures, "cerebral paralysis," paralysis of the face and upper limb, and atrophy of muscle groups.

4. Involvement of the peripheral nervous system.

Symptoms referable to the peripheral nervous system are common. Chief among them are paresthesias or radiating pains in the region of distribution of the intercostal and lumbar nerves, the limb plexuses, and the sciatic, trigeminal, facial and occipital nerves (CATSARAS 1890; KEAYS 1909; KLIENEBERGER 1907; LIE 1904; PARKIN 1904; SILBERSTERN 1895). Such pains may last for several days and persist after all other symptoms have disappeared (BAUER 1870). Unilateral migraine-like pain may also occur (MICHEL 1880). Oculomotor nerve palsy has also been observed (GERBIS and KOENIG 1939).

5. Peripheral edema.

Edematous swelling of the extremities quite distinct from swelling in the region of joints is fairly common in the early stages of decompression sickness. The arms or the legs or one arm and the leg of the other side, etc. may be affected. The circumference of a limb may be increased by as much as 5 cm. As a rule the swelling disappears in 3 to 5 days. (HELLER 1895; HELLER et al. 1895; KEAYS 1909; KOENIG 1939; LUCKE 1941.)

6. Cerebral involvement.

Signs and symptoms of cerebral involvement are fairly frequent and are usually combined with clinical evidence of spinal cord involvement. BORNSTEIN (1914) reported cerebral disturbances in 10% of cases, and LUCKE (1941) stated that next to bends, symptoms of CNS involvement stand uppermost in the list of manifestations of decompression sickness. Such disturbances are virtually always transitory, and include confusion, delirium, hallucinations, mania, amnesia, unconsciousness, asphasia of various types, agraphia, blurring of vision, blindness, extraocular muscle palsies, hemianopia, involuntary ocular movements, and convulsive seizures (BABINGTON and CUTHBERT 1863; BOINET 1906; CATSARAS 1890; DRASCHE 1898; GERBIS and KOENIG 1939; HELLER et al. 1900; HOCHE 1897; MCCALLUM and WALDER 1953; MICHEL 1880; OLIVER 1899; PARKIN 1904; SILBERSTERN 1895). Aphasia is particularly common and sometimes occurs as an isolated symptom (HELLER et al. 1900). *Hemiplegia* with or without facial involvement has now and then been reported as due to cerebral involvement (CATSARAS 1890; CHABAUD 1883; DOMÍNGUEZ 1912; VON HALLERSTEIN 1889), but in some of these cases the weight of evidence favors a double monoplegia of spinal cord origin. Loss of mimetic facial movements in the presence of intact voluntary facial movements has been observed (DRASCHE 1898).

7. Ocular changes.

Papilledema has been noted on occasion (CALLAN 1907; GERBIS and KOENIG 1939; KLIENEBERGER 1907; PICK 1904), as has also partial optic atrophy (GENET 1933; LUCKE 1941).

B. Syndromes.

The disabilities incurred by the diver and the caissonier and of the miner who works under compressed air are capricious and unpredictable. In workers taken ill under the same circumstances the onset in some is insidious and in others fulminant, as pointed out by GAL as long ago as 1872. A diver may rise to the surface appearing little the worse for his submersion and yet an hour later he may be in a hospital powerless and in racking pain. Or on reaching ground level his appearance may be alarming, but on the next day he is ready to go down again. The wide diversity in the syndromes encountered is illustrated in the following.

1. Progressive asphyxia culminating in shock.

After decompression, an hour or two of well-being may elapse when a sensation of substernal distress (chokes) signals approaching asphyxia. Or, on the other hand, there may be respiratory and circulatory distress by the time the individual reaches ground level. In either event, cyanosis of the entire body (with mottling of the skin) and embarrassment of respiration in the inspiratory stage are evident. Tachypnea also occurs. Paroxysmal attacks of coughing (advanced chokes) accentuate the asphyxia. Shock develops and the pulse may be shallow, fast and arrhythmic, or it may be little altered and even slow (BEHNKE 1951; BORNSTEIN 1918; HELLER et al. 1895; STETTNER (1911). The heart may be dilated (HORNUNG 1901), on auscultation of the heart a rumbling sound *(gargouillement)* may be heard (CATSARAS 1890), and pulmonary edema may be evident (KOENIG 1939; MCCALLUM and WALDER 1953). Muscle spasms and convulsions sometimes occur. Petechiae have now and then been encountered in mucous membranes (HIRT 1874; KOENIG 1939; STETTNER 1911). Any signs of focal

CNS damage that may have developed are overshadowed by coma. The period of greatest danger is the first 15 minutes (SCHERSTÉN 1948). In individuals who recover there may be bradycardia for as long as 3 weeks, with the heart rate as low as 30 per minute (STETTNER 1911).

2. Unconsciousness culminating in shock.

On reaching ground level or a short time afterward the individual suddenly drops to the ground unconscious as if shot. Neither dyspnea nor cyanosis serves as a warning signal. During the period of unconsciousness, which may last for several hours, there may be signs of focal CNS involvement. Shock ensues, and it may deepen until fatal.

3. Delayed progressive shock.

For an hour or two following decompression, bends are the only conspicuous symptom. The individual is anxious. Soon the skin becomes cold and clammy and the pulse and respiratory rates elevated. Inspiration is deep and prolonged and expiration short and shallow, but there is no dyspnea. No coughing occurs. The blood pressure falls. There is no dulling of the individual's interest in the surroundings. The right side of the heart becomes dilated and the heart sounds feeble, and no murmur is heard. The blood pressure continues to fall. Restlessness develops and the patient becomes incoherent, then maniacal. Hemoconcentration becomes evident. The respirations grow shallow, stertorous, and jerky, and deepening cyanosis brings death.

In a case of this kind described by RUDGE (1907), of a diver who had been at 25 fathoms (150 ft.) for 5 hours and been decompressed at the conventional rate, death occurred in about 22 hours. No paralysis was detected, nor were there changes in sensibility or the reflexes. The story was not essentially different from that in Case 1 in Table I (p. 1614), in which death followed decompression to altitude.

Autopsy was begun in 15 hours. The subcutaneous fat was excessive and greasy, and it was red and mottled like fresh bone marrow. The omentum had the same appearance, and on being cut it yielded yellow oily fluid which escaped into the peritoneal cavity. Numerous bubbles were found in the omental fat, and variable numbers in gastric veins, coronary veins, right ventricle, renal vein, innominate arteries, cut surface of the liver and kidney, and synovial fluid in the knee joint. The brain was described as normal. The spinal cord was not examined.

4. Fulminant spinal cord involvement.

In this category are included the cases in which spinal cord involvement dominates the clinical picture from the start. The scope and severity of the spinal symptoms vary widely, and duration of incapacitation is unpredictable. In the series of cases reported by BAUER (1870) respirations were "invariably undisturbed." The onset may be gradual and marked by an ill-defined generalized hyperesthesia of the lower half of the body or it may be sudden and dramatic, as in the following cases.

Upon leaving a caisson in which he had been under 3 atmospheres of pressure, a worker felt well for about one-half hour. He then became dyspneic and experienced a feeling of pressure in the region of the heart, whereupon he fell to the ground and was unable to move his legs. Urinary retention developed at once. (LEYDEN 1878.)

A caisson worker completed his 2-hour shift, and "on emerging from the caisson he drank some coffee, took a hot bath, and entered a boat to be carried across the river. On trying to rise from his seat—this being a half hour after coming out of the caisson—he found that he was unable to move his legs and that they felt numb. He had to be carried to the hospital". (VAN RENSSELAER 1891.)

C. Course and the incidence of fatality.

Nowadays the course of the sickness is usually brief, for immediate and sufficiently prolonged recompression usually brings about rapid recovery, even from paraplegia. The CNS symptoms in decompression sickness are not progressive, but they may crop up anew in different regions (BOYCOTT et al. 1908; OLIVER 1899). Actually the CNS disorders always recede with time. Insufficient recompression may be followed by residual signs and symptoms of spinal cord involvement for several weeks or even permanently (BABINGTON and CUTHBERT 1863; BAUER 1870; CHARPENTIER 1883; DE MÉRICOURT 1868; VON HALLERSTEIN 1889; KLIENEBERGER 1907; LICHTENSTEIN and ZEITLIN 1936; MCCALLUM and WALDER 1953; MICHEL 1880; MINKOWSKI 1912; PARKIN 1904; SJÖBLOM 1925). Permanent impairment of cerebral function has been reported, but is exceedingly rare (BORNSTEIN 1914).

Before the lock was used in caisson work and the MOMSEN "lung" in diving, the mortality rate in decompression sickness was as high as 25% (THORNE 1941). Building a bridge across the Mississippi River in 1875 cost 119 casualties among 352 workers; among these some 30 were seriously ill and 12 died (CLARK 1870). Pearl diving has also taken its toll. Of 140 cases of paralysis among pearl divers reported by BLICK (1909), death occurred in 11—in 8 of these as a result of septicemia consequent to *sloughing and cystitis, and in 3 from supervening* meningitis. Of 92 fatal cases collected from the literature up to 1900 by HELLER et al., death occurred *immediately* in 28, in *2 hours* in 13, *2 to 24 hours* in 18, *2 to 14 days* in 13, *2 to 4 weeks* in 5, *1 to 3 months* in 10, *3 to 7 months* in 4, and *after 2 years* in 1. (A detailed analysis of the morbidity and mortality data of HELLER et al. is given by VON LELIWA [1909].)

D. Hematological, CSF and visceral changes.

As much as 30 per cent increase in blood volume has been observed by BEHNKE et al. (1936) in dogs rapidly decompressed after exposure to high atmospheric pressure (60 pounds gauge for $1^1/_2$ hours). Hemoconcentration has also been observed in man (RUDGE 1907). Sludging of blood has been seen in the pial vessels of living animals upon decompression but only after vascular occlusion by gas bubbles, suggesting local ischemic anoxia as the cause (VILLARET et al. 1937; WAGNER 1945). Petechiae in mucous membranes are a fairly common feature (HIRT 1874; STETTNER 1911). CSF fluid was unaltered in one case in which it was examined (KLIENEBERGER 1907).

In experimental animals and man the pulmonary changes have included edema and congestion and hemorrhage into alveolar walls and/or air sacs (BERT 1878; HELLER et al. 1900). In severe cases in which the pulmonary artery was choked with bubbles and the right heart distended, the lungs have been found pale and bloodless (BOYCOTT et al. 1908). Transudate in pleural and pericardial sacs appears to be uncommon. The mucous membrane of the small intestine sometimes has the appearance of "small grains of tapioca placed closely together in patches," due to the presence of small gas bubbles in the submucosa (LEVY 1922). Watery vacuoles have occasionally been observed in hepatic cells (HILL 1912; GERSH et al. 1944b). Osteoarthritis is a frequent complication (CHRIST 1934; COLEY and MOORE 1940; PLATE 1912; TAYLOR 1943).

Fat embolism in the lungs and brain in a case of diver's sickness has been reported by HAYMAKER and JOHNSTON (1955).

Case 13 (AFIP Acc. 150191). This diver (180 lb., 5 ft.) descended to a depth of 202 ft. (72 m.) for an undetermined period of time and was brought up apparently in a routine

manner, but lost consciousness and was recompressed several times without avail. Death occurred 6 hours after the onset of symptoms.

At autopsy, which was performed 14 hours after death, the heart was found to contain frothy, dark-red, thick blood. Innumerable gas bubbles were present in many tissues and in veins. Petechiae were also widespread. There was no pleural effusion. The lungs together weighed 1400 gm. All lobes were soft, subcrepitant, heavy, and dark-red. Oil-red-O stained sections revealed many fat emboli in pulmonary vessels. There were as many as 10 to 12 fat emboli to the average-sized section on a 3″ × 1″ slide. The cerebral cortex and brain stem presented edema and venous and capillary engorgement. Perivascular hemorrhages were encountered in the lateral part of the medulla oblongata. The IXth and Xth nerves showed myriad vacuolar spaces in myelin sheaths and endoneurium, the significance of which was not determined. The spinal cord appeared normal.

The incidence and the cause of the fat embolism are presented on pages 1613, 1630, 1646 and 1656.

E. The brain in air embolism.

Since air embolism and the gas bubble embolism of decompression sickness have close pathogenetic similarities and since air embolism may be a feature of rapid or explosive decompression, it will be advantageous to review briefly the cerebral changes which have been observed in air embolism. In dogs from which the skull cap was removed, MAGNUS and JACOBI (1925) observed profound constriction of pial vessels after 2 cc. of air were injected very slowly into the carotid. Even vessels remote from those embolized exhibited maximal constriction. On the other hand, in watching pial vessels of dogs through a FORBES-WOLF window implanted in the skull, VILLARET et al. (1937) were struck with the absence of vasomotor changes. They noted that under minimal conditions of air embolism, tiny bubbles were carried along in the center of the arterial blood stream without interfering with the blood flow. When, however, larger quantities of bubbles were present they collected in columns which were pushed along in the blood stream as far as the capillaries, where they adhered to the walls, slowing or halting the flow of blood. BROMAN (1940) found in cats that air emboli entering the pial circulation traversed vessels in 10 to 20 minutes and disappeared.

Data on the very early cerebral vascular responses in guinea pigs receiving 0.3 cc. of air (in the form of foamy blood) via the carotid artery have been provided by HARTER (1947). In animals sacrificed *5 minutes* after the introduction of the air, numerous vascular filling defects (brought about by irregular angiospasm) were observed in the terminal capillary network as well as in small and large veins and in arteries, particularly in the cerebral cortex. The angiospastic reaction had also occurred outside the embolized region. At the $^1/_2$ *hour* stage the defects had disappeared. At *2 hours* the capillary network was again filled with blood, though to a degree suggesting hyperemia. At *12 hours and 10 minutes* there were only „feinkörnige pericapilläre Höfe" together with petechiae and hemoglobin deposits near capillaries. At *2 hours and 40 minutes*, ischemic cell changes were visible. At *24 hours* there were still signs of angiospasm—a delayed reaction considered to be as conducive to parenchymal damage through ischemia and anemia as the initial angiospasm.

In a dog which was sacrificed *22 hours* after the injection of 3 to 4 cc. of air into the carotid, BODECHTEL and MÜLLER (1930) found hemorrhages in the meninges and both focal and diffuse ischemic cell changes in the cerebral cortex. In a similar experiment in which the dog died *24 hours* after receiving 10 cc. of air via the carotid, RÖSSLE (1944) noted, among other changes, abundant clotted plasma perivascularly, and in one region of the white matter in which hemorrhage had occurred there was an abundance of leukocytes in the parenchyma, reminiscent of hemorrhagic encephalitis. In studies of the brains of monkeys which received air by way of the carotid, SPIELMEYER (1913) observed in an animal surviving *4 days* numerous round, oval or wedge-shaped pallid foci *(Erbleichungen)* in the upper and middle laminae of the cerebral cortex in which nerve cells had been destroyed and astrocytes had undergone striking proliferation. Gliosis was also apparent at the periphery of such lesions. The earliest changes observed, at *15 hours*, consisted of ischemic nerve cell changes (including "incrustation of the GOLGI net") in the same cortical laminae as seen on the 4th day. At *3 weeks* the foci were intensely gliotic.

Changes of a similar nature have been observed in *man*. KÖHN (1952a) has pointed out that with the passage of time the necrobiosis brought about by air emboli becomes more severe, edema fluid is resorbed, and, in 1 to 4 days, glia multiply, vessel walls undergo hyperplasia, and new capillaries form. In a case in which death occurred about *5 minutes* after air embolism, CHASE (1934) observed small perivenous hemorrhages in the frontal and parietal lobes, venous plasma stasis, and collapsed arteries and capillaries. At *7 hours* after air embolism, SPIELMEYER (cited by NEUBÜRGER 1925) found regressive changes in nerve and

glial cells together with parenchymal edema and tiny petechiae. RÖSSLE's (1944, 1948) *7-hour* case was characterized in addition by pallor of the walls of precapillaries and capillaries of the cortex, necrosis of vessel walls of the white matter, and extravasation of plasma perivascularly, especially in the white matter. In a case of *21 hours'* duration, KÖHN (1952a) found gitter-cell-containing necrotized foci in the cerebral cortex, adjacent to which leukocytic meningitis had developed; also there were a few parenchymal petechiae and an occasional ring hemorrhage. At *24 hours*, WEISSENRIEDER (1934) noted similar changes, and, in addition, hyaline capillary thrombi, numerous perivascular hemorrhages, and copious serofibrinous exudate perivascularly and in the adjacent parenchyma. In a case of *27 hours'* duration described by SCHNITTERT (1939), focal perivascular ischemic cell changes in the brain were virtually limited to the cortex. An important feature in SCHULMAN'S (1954) *36-hour* case was that some of the ischemic infarcts were elongated and extended from the white matter directly into the cortex, where they assumed a wedge-like shape. In a case of *55 hours'* standing in which the foramen ovale was open, NEUBÜRGER (1925) reported relatively large, well delimited, round, oval or wedge-shaped perivascular foci in the cerebral and cerebellar cortex in which nerve cells were the seat of ischemic necrosis. The degree of alteration in different lesions varied. Within some foci there were reactive changes in neuroglia and apparently in HORTEGA microglia. None of the microglia contained free fat. At the periphery of some foci, astrocytes had undergone slight reactive changes. The blood vessels in some foci appeared unaltered and in others the endothelial cells showed regressive changes. Occasional petechiae were noted in the cortex and in some of the foci there was evidence of edema perivascularly. In addition, rather extensive areas of the cortex showed regressive changes of laminar distribution. In a case of massive air embolism following therapeutic pneumothorax reported by AMEUILLE et al. (1935) in which the patient died on the *21st day*, changes of a similar character were noted, and, in addition, many large, more or less confluent petechiae in the subpial cortex and subcortical white matter and infiltration of hemorrhagic areas by abundant leukocytes.

In their cases of air embolism, RÖSSLE (1944, 1948), LOESCHCKE (1950), FELIX and LOESCHCKE (1950a and b) and SCHUBERT (1951) went to some length in describing widened VIRCHOW-ROBIN spaces, bubbly perivascular clotted plasma, and a bubbly appearance of ependymal cells, and claimed that these changes can be taken as evidence of the diffusion of air through vessel walls. (The vacuolar appearance of the perivascular clotted plasma was not unlike that in our Fig. 21B.) This interpretation has been vigorously countered by KÖHN (1952a and b, 1953).

LHERMITTE and BARRELET (1934) have had occasion to examine the brain of an individual who suffered a left hemiplegia due to air embolism following the nicking of the left jugular vein in the course of partial cervical sympathetic ganglionectomy. Immediately after the incident a mill-wheel sound, characteristic of the presence of intracardiac air, could be heard over the heart. Upon removal of the dressings from the wound 8 days later the hemiplegia recurred and the patient became comatose. During the ensuing days, in which the patient gradually recovered consciousness, a positive Babinski reflex was elicited on the right side. About *2 months* later the patient died from bronchopneumonia. The foramen ovale of the heart had closed. In the frontal and parietal lobes, especially in the precentral gyrus, laminae I and II showed generalized parenchymal sponginess with loss of nerve cells and fibers, and elsewhere there were numerous tiny perivascular foci of sponginess from which nerve and glial cells had disappeared and in which vessel walls showed reactive changes. Moreover, there was a diminution of BETZ and other pyramidal cells and in the postcentral gyrus a complete loss of nerve cells from laminae II and III with replacement by macroglia and microglia.

F. The brain in decompression sickness.

In both experimental animals and man, relatively little on the subject of cerebral changes in decompression sickness is to be found in the literature. VON SCHRÖTTER'S (1906) monograph is one of the best sources. HELLER et al. (1900) observed nothing noteworthy in the brains of the many paraplegic dogs they studied, but there is no way of determining how carefully these brains were examined. Petechiae or larger hemorrhages into the brain have occasionally been noted in man (BERT 1879; BLICK 1908; CATSARAS 1890; WIETHOLD 1936), but almost always in association with hemorrhage into the spinal meninges or spinal cord. In the case described NORDMANN (1928), death occurred in a *few minutes* after decompression following a 15-hour exposure to 1.3 to 1.4 atmospheres. During the previous day the patient had had bends and abdominal pains

following decompression. Histological examination revealed widespread perivascular (capillary and venous) hemorrhages in the cerebral grey and white matter. The basal nuclei were chiefly implicated: adjacent to many of the perivascular hemorrhages there were plasma-laden foci in which the nerve cells were necrotic and in which "glial fibers" were severely damaged. No glial reaction was apparent. (The spinal cord changes are described on page 1636.)

Hemorrhage into the brain also characterized the case described by LIE (1904), in which the course of the sickness ran for *3 days and 13 hours.*

This individual, for 15 years a diver, had taken 3 dives to depths of 124 and 154 ft. (39 and 47 m.) in a single day, and upon emerging from the third dive he suddenly became dizzy and suffered some loss of consciousness. This episode soon came to an end, but he was left with total paraplegia and pains in the sacral region and both arms. Touch and appreciation of pain in the lower limbs were preserved. On the 2d day, paresis of the arms (without anesthesia) was noticeable. By the 3d day the paraplegia was unaltered, but now there was complete anesthesia up to Th 5. Pains in the arms persisted throughout the course. On the 3d day the pulse rose and coma and death ensued.

Autopsy disclosed many petechiae and ecchymoses in the epicardium, endocardium, pleura, and gastric mucosa. Petechiae were widespread in the cerebral white matter, but were present chiefly in the more rostral part of the occipital lobes and in the region adjacent to the basal nuclei. Microscopic examination disclosed numerous minute softened areas in the white matter, most of them hemorrhagic. Ring hemorrhages were common. Some cerebral nerve cells contained abundant pigment, the nature of which was not disclosed.

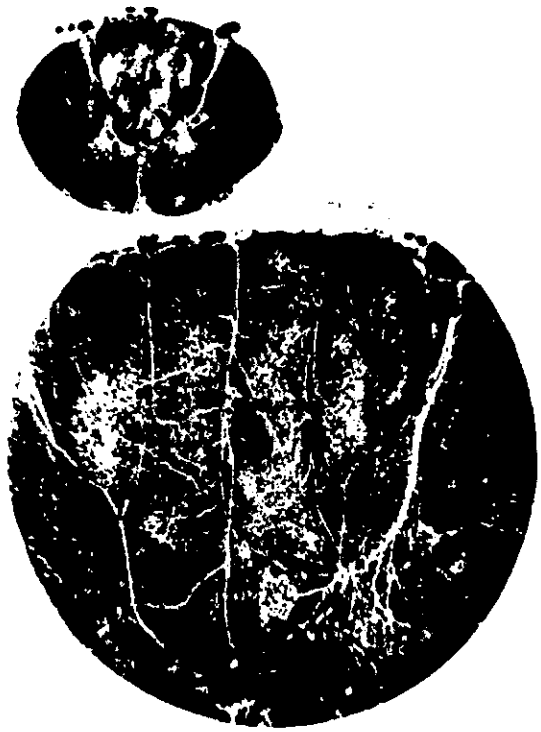

Fig. 9. Case of diver's sickness of 3 days and 13 hours' duration. From an upper thoracic level, showing numerous areas of ischemic necrosis of the white matter, particularly in the posterior columns. An enlargement of the posterior columns is shown on the lower photograph. VAN GIESON stain. (From LIE 1904.)

Gross inspection of the cord disclosed a suggestion of softening at upper thoracic and lower cervical levels, and in these regions there were numerous petechiae and reddened foci. Microscopically, numerous minute hemorrhages were seen in the cervical enlargement of the cord, predominantly in the white matter. Here, too, there were numerous softened foci in which axis cylinders were swollen. The upper thoracic cord bore the brunt of the insult (Fig. 9). A few small mononuclear cells were seen perivascularly. Some nerve cells contained an excess of pigment. The central canal contained erythrocytes and was somewhat dilated. A few petechiae were noted in the medulla oblongata.

Examination of *posterior spinal roots* disclosed numerous atrophic nerve fibers and moderately proliferated connective tissue. The *anterior roots* showed nothing of significance except for occasional suggestive degeneration in MARCHI preparations. In the *sciatic nerve* and *brachial plexus*, changes similar to those in the posterior roots were observed.

Paucity of changes in the central nervous system in acute diver's sickness is illustrated in the following case which came under our observation (HAYMAKER and JOHNSTON 1955).

Case 14 (AFIP Acc. 164136). The subject (165 lb., 5 ft. 10 in.), equipped with a shallow-diving outfit (face mask and hose), had been engaged for an undetermined period of time in diving activities at a depth of 54 ft. (16.6 m.) under a pressure of 26 pounds. He responded to signal, and 10 minutes later, on being brought to the surface, he was unconscious. He was lifted into the ship and was soon pronounced dead.

Autopsy was begun $5^1/_2$ hours after death. Transection of the superficial vessels was attended by outpouring of bubble-laden blood. The pericardial cavity contained approximately 20 cc. of fluid. Frothy blood was present in the cardiac chambers. The lungs were emphysematous. Innumerable gas bubbles were found in mesenteric, retroperitoneal and pelvic veins. The periadrenal fat tissue was dotted with petechiae. Microscopically, many air sacs of the lungs were found filled with edema fluid. No fat emboli were observed. The brain was congested. In the cerebral white matter there were many small perivascular foci of edema with myelin damage. The adventitia of occasional vessels in the caudate nucleus was raised bubble-like from the muscularis. Throughout most of the cross-sectional area of the pons and medulla oblongata, the perivascular spaces were unduly distended, and the surrounding parenchyma was spongy, with the spongy zones sometimes extending finger-like for a considerable distance from vessels. Clotted plasma was occasionally seen in perivascular spaces. Cranial nerves showed myriad vacuolar spaces both in nerve fibers and in endoneurium, the significance of which was not determined. The spinal cord was not available for study.

G. Spinal cord.

1. Experimental animals.

The classical studies of HELLER, MAGER and VON SCHRÖTTER (1900) are worthy of citation in some detail. Most of their observations were on dogs compressed to about 4.5 atmospheres (150 ft.; 45.7 m.) for an hour or so and then suddenly decompressed. Paralysis of the hind limbs usually developed in a few minutes and persisted, and the animals either died or were sacrificed.

In animals which died or were sacrificed within 10 minutes, nothing of significance was seen in the spinal cord. At the 1-hour stage only petechiae were found. Animals surviving 5 days or longer usually displayed ischemic lesions in the spinal cord. The segments of predilection were the thoracic and upper lumbar although those of the cervical region were occasionally most implicated (Fig. 10). The white matter bore the brunt of the attack, with the lateral columns being most consistently and severely involved, the posterior columns less frequently, and the anterior by far the least. Lesions of the grey matter were said always to be coextensive from the white matter, but from the many illustrations provided it appears that the grey matter, too, was sometimes primarily involved.

In the white matter the lesions were of two kinds: 1. spongy transformation with subsequent gliosis and 2. frank necrosis with eventual cavity formation. In early stages, focal areas of white matter displayed disintegrative changes in myelin and swelling of axis cylinders (as much as 30 times), associated with a widening of the tissue interstices *(Lückenfelder)* (Fig. 11A). A similar alteration was sometimes visible at the edge of frankly necrotic foci (Fig. 11B). Radiating networks of "condensed ground substance," presumably the fibers of proliferated glia, gave the cord a patchy sclerotic appearance (Fig. 12A). Some nerve fibers had undergone regressive changes and resorption, accentuating the parenchymal sponginess. In the more advanced lesions the parenchymal architecture was erased, with the formless parenchyma being converted into detritus intermixed with gitter cells and balls of myelin.

In early stages of evolution the excavated necrotic areas had an irregular border because of the projection into them of shreds of cord tissue and the remains of vessels (Fig. 12B). Later the border took on a smooth sclerotic appearance and in time the wall of the cavity underwent glial proliferation.

The *grey matter* was affected in a different manner. Nerve cells undergoing vacuolization and other regressive changes were commonly found in otherwise intact grey matter (Fig. 13). Exceptionally, focal areas of the grey matter were totally destroyed.

When viewed in cross section, the lesions in the spinal cord were sometimes wedge-shaped with the base of the wedge parallel to the periphery of the cord

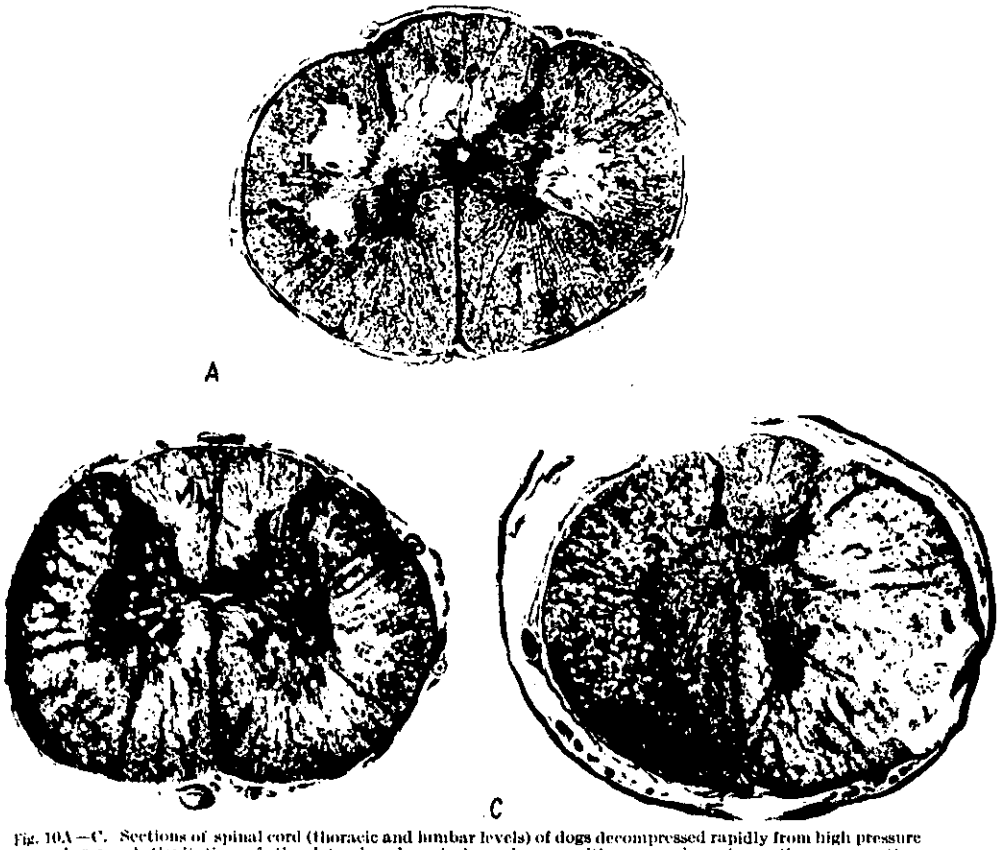

Fig. 10A—C. Sections of spinal cord (thoracic and lumbar levels) of dogs decompressed rapidly from high pressure atmospheres. A Cavitation of the lateral and posterior columns with encroachment on the grey matter. B Sponginess completely surrounds the grey matter. C Almost complete necrosis of the anterior and lateral columns of one side with less severe necrosis of the lateral column of the other side. (From HELLER et al. 1900.)

(Fig. 10A). Although the lesions were usually limited to the more central part of the white matter (Figs. 10A and B), they sometimes extended to the pia (Fig. 10C). Cavity formation appeared to represent a confluence of smaller focally-involved areas: in longitudinal section the cavities were either symmetrically tubular or tortuous (Fig. 12B). Secondary degenerative changes in ascending and descending tracts were evident within one month after the animals had been decompressed. There were never any large hemorrhages in the cord, and when petechiae were found they were evidently of a secondary character.

2. Man.

The spinal cord is also a site of predilection of lesions in man. The thoracic segments of the cord are most often affected, and frequently the lesions are

limited to these segments. Upper lumbar segments are less often involved and cervical segments the least (BLANCHARD and REGNARD 1881; CATSARAS 1890; HELLER et al. 1900; VAN RENSSELAER 1891; ZOGRAFIDI 1907).

Little more than *hemorrhage* has been noted in the spinal cord in rapidly fatal cases of decompression sickness. Thus, in the case described by NORDMANN

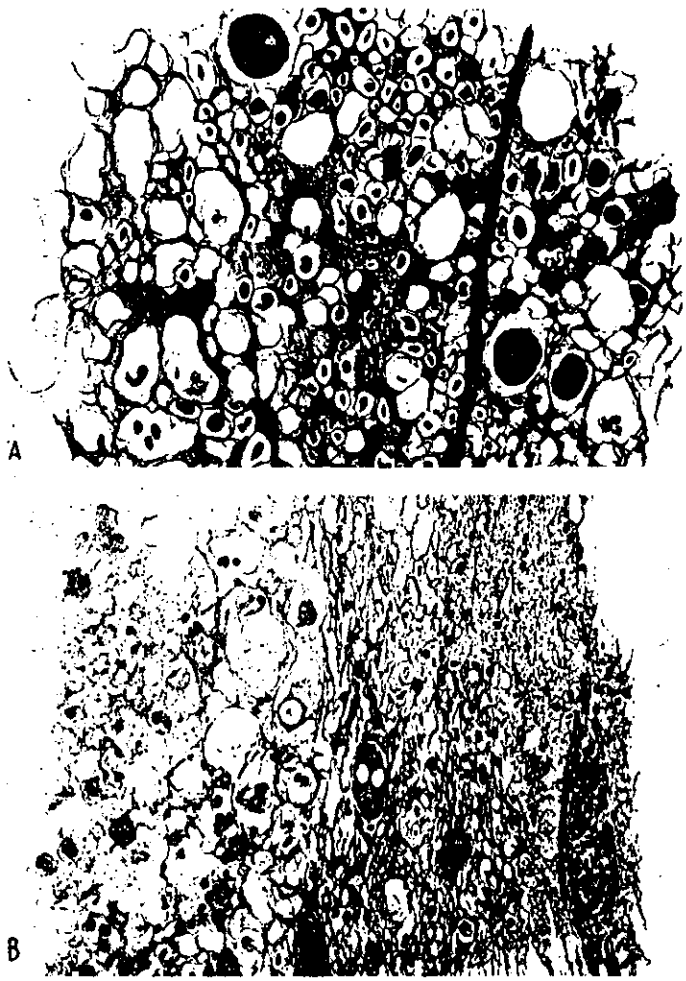

Fig. 11 A and B. From the spinal cord of a dog which died 16 days after compression-decompression. Five minutes after reaching ground level the dog drew up its right hindlimb, stood with both hindlimbs rigidly extended, then fell over. Paralysis and anesthesia of the hindlimbs persisted to the end. A. A field of white matter of an upper lumbar segment. The tissue has undergone spongy transformation. Numerous axis cylinders and their myelin sheaths have disappeared and some that remain are tremendously enlarged. B. From segment Th 3 to 5 of the same animal, showing the wall of a detritus-containing cavity in the white matter. Much of the wall is necrotic. (From HELLER et al. 1900.)

(1928), referred to on page 1633, only a few petechiae were found in the white matter, and then at the periphery of the cord. Not even hemorrhage was found in 2 cases of *2 and 7 hours'* duration respectively, reported by HELLER et al. (1900). Hemorrhage was a salient feature in pearl divers autopsied by BLICK (1909). Most of the deaths had occurred acutely. Hemorrhage practically severing the lower cervical cord was noted in some 9 cases, and in these, as in other cases, the subdural space almost always contained blood or blood-stain-

fluid, and the meningeal vessels were engorged. In this series of cases the lower cervical region was the divers' calx Achillis, for only in this region was the cord disintegrated. In a review of the literature before 1900, LÉPINE stated that *hematomyelia* occurred habitually in divers, but he gave few concrete data.

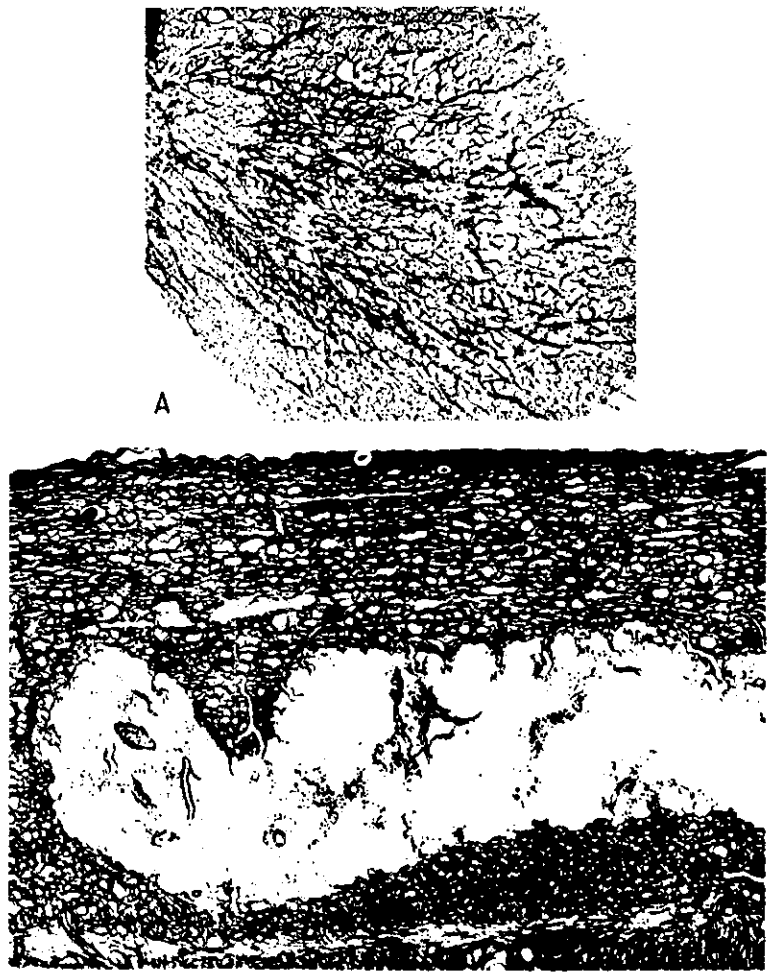

Fig. 12 A and B. From the spinal cord of a dog which died on the 34th day after compression-decompression. The animal appeared normal for the first 15 minutes, when it suddenly fell to the ground, with its hindlimbs beset with extensor spasms. After another 10 minutes the forelimbs became similarly affected, and respirations were superficial and heart action rapid and irregular. Subsequently the hindlimbs became completely paralyzed and anesthetic. There was multiple focal damage of the white and grey matter, consisting chiefly of focal cavity formation at most levels from Th 1 to L 2. A. An area of white matter composed of radiating, "condensed ground substance" (presumably glial fibers). B. Longitudinal section illustrating the tubular shape of a detritus-containing cavity in the white matter. Vessels jut into the cavity. (From HELLER et al. 1900.)

Small subarachnoid and/or dural hemorrhages have been noted in 3 or 4 cases reported by CLARK (1870) in caisson workers.

In a review of autopsied cases of caisson worker's and diver's sickness up to 1891, VAN RENSSELAER was able to find 25 examples, but there were only 3 of these in which the CNS had been studied microscopically (the cases of BAUER, LEYDEN and SCHULTZE, referred to herein). In all 25 the brain appeared normal or was congested. *Extravasations of blood* on the external surface of the dura

were seen in about one-third of the cases. There was thrombosis of a lepto-meningeal vein near the cauda equina in one instance of *9 days'* duration (JAMINET 1871), and a subarachnoid effusion of blood compressing the lumbar enlargement in another. In virtually all the 13 spinal cords available the lower thoracic segments were softened, and frequently the upper lumbar segments as well. In one case all the spinal cord up to segment C 5 was softened to a pulp.

Changes of a similar hemorrhagic character have been noted by ZOGRAFIDI (1907). In 3 cases, in which the course ran *2, 5 and 16 days* respectively, there were multiple extravasations of blood or foci of hemosiderin-laden macrophages

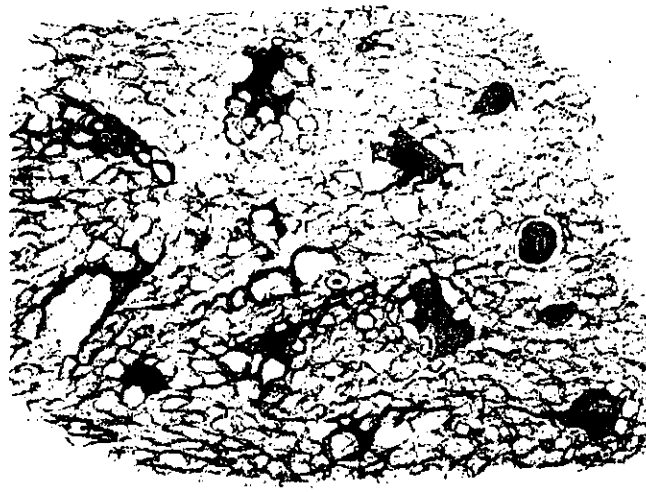

Fig. 13. From a dog which died 10 days after its last decompression. Striking regressive changes in nerve cells of an anterior horn. The nuclei of most of the nerve cells have disappeared and the cytoplasm has become vacuolated or been converted into stringy masses. (From HELLER et al. 1900.)

both in the white matter and the grey; in 2 of these the lesions involved the cervical region, though less severely than at lower thoracic and upper lumbar vessels. In a diver who ascended rapidly from 32.8 fathoms (60 m.) and who died on the *12th day*, the grey and white matter of the lower thoracic segments was ripped to pieces—in cross sections constituting little more than irregular islands of tissue. In an adjacent segment the region of the dorsal horn was blown up into a large, totally necrotic oval focus—appearing like a walled-off abscess—and a little higher, identical foci were present in the region of both posterior horns. The upper lumbar segments were affected, but less severely. Disintegrative changes of about the same extent and degree were noted in another case, and in the posterior columns alone in still another.

Severe hemorrhage has also been noted in cases of relatively long standing. A case in point is that described by COTSONOPOULOS (1871), in which paraplegia associated with anesthesia of the lower limbs and paralysis of the bladder developed in an hour after a dive to 100 ft. (30 m.). Death occurred *40 days* later. Profuse hemorrhage was found epidurally along the entire length of the vertebral canal and a smaller quantity of blood in the subarachnoid space of the lower spinal canal as well; also most of the white matter of the lower thoracic and upper lumbar segments was softened.

Scattered hemorrhages in the cord were a feature of the case of *48 hours'* duration reported by NIKIFOROFF (1893). The caisson worker lost consciousness immedi-

ately after decompression and soon afterward cyanosis and extreme restlessness set in and the pulse became very weak and the heart sounds faint. At autopsy the lateral and particularly the posterior columns of the thoracic segments were characterized by many punctate and slightly larger red-brown areas, some excavated. Carmine-stained sections revealed numerous poorly-stained areas—some around vessels—from which many nerve fibers had disappeared. The cavities observed in longitudinal sections were oval and had irregular edges. Axis cylinders in the involved parenchyma were disrupted and were swollen to as much as 20 times their normal size. Scattered in the white matter were dense networks referred to as sclerotic ground substance, similar to those illustrated in Fig. 12A. A diffuse plasma transudate was seen in the grey matter, and tiny hemorrhages in both grey and white. Gitter cells were absent and there were no leukocyte infiltrates. The nerve cells were intact save for regressive changes. The cervical and lumbar segments appeared normal, as did also all the spinal roots examined. Similar changes were noted in the case of LIE, of 3 days and 13 hours' duration, described on page 1633.

Remnants of old hemorrhage also characterized LEYDEN's (1878) case. This concerned an individual who, after several hours in a caisson at 3 atmospheres, had been decompressed in $^1/_2$ hour. Death occurred on the *15th day*.

One-half hour after leaving the caisson, he suddenly experienced a sensation of pressure over the chest and difficulty in breathing, and his legs gave way. Urinary retention set in. There was total flaccid paraplegia and sensory loss up to the lower border of the thorax, most pronounced on the right. The right cremasteric reflex was reduced. During the subsequent course the paralysis and anesthesia persisted. Mental acuity remained unaffected until the end.

At autopsy the brain appeared normal. There was striking engorgement of spinovertebral and meningeal veins and rather abundant clear fluid in the subdural space. On cross section the white matter appeared swollen, especially at thoracic levels. On microscopic examination, involvement of the spinal cord was said to be limited to the white matter of the dorsal and dorsolateral parts of the thoracic segments (Fig. 14), except for minor changes in ventrolateral and ventral parts. Affected levels were speckled by yellow tinted lesions from which all parenchyma had disappeared and been replaced by well circumscribed pools of fat-free gitter cells, in the midst of which the fully intact blood vessels were visible. Glia were said to be normal in appearance and number. Much of the white matter of the dorsal half of the cord was finely spongy, contained enlarged axis cylinders, and had a curious net-like appearance. No changes were observed in the grey matter of the cord or in the spinal roots.

In some cases of decompression sickness, particularly those of relatively long duration, multiple softening without evidence of hemorrhage has been the outstanding feature. To be included here is the case of a caisson worker presented by BAUER (1870), which to our knowledge is the first autopsy report of decompression sickness. Death occurred *5 days* after decompression. The spinal cord exhibited characteristic softenings, but the observations of particular interest were those on exposing the spinal cord.

In dissecting down through the paravertebral muscles the vascularity signally increased with the approach to the spine. "On removing the vertebral arches and exposing the dura mater, the cellular tissue exhibited great vascularity, and a reddish, gelatinous infiltration. The dura mater was separated from the cord by a copious collection of serum [about 2 ounces], fluctuating on pressure and changing its level on altering the position of the body ... In pressing on the spinal cord some resistance was observed, which proved to be serum in its canal. So much had accumulated in that space that being pressed from two opposite directions, it would distend the cord cylindrically. Near the cauda a moderately sized vein was completely thrombosed."

VAN RENSSELAER'S (1891) case was one in which total paraplegia together with anesthesia of the lower limbs lasted *36 days*. The mid-thoracic segments were most affected, especially the posterior and lateral columns. Within the punctate lesions seen grossly, many nerve fibers had been destroyed. Blood vessels in affected areas were thickened and surrounded by mononuclear cells. Ascending and descending spinal degeneration was pronounced. No evidence of hemorrhage was found.

The report of VON SCHROETTER (1904) deals with his observations of 3 spinal cords of divers sent him by Professor SAVAS, of Athens. *One* of the divers, upon

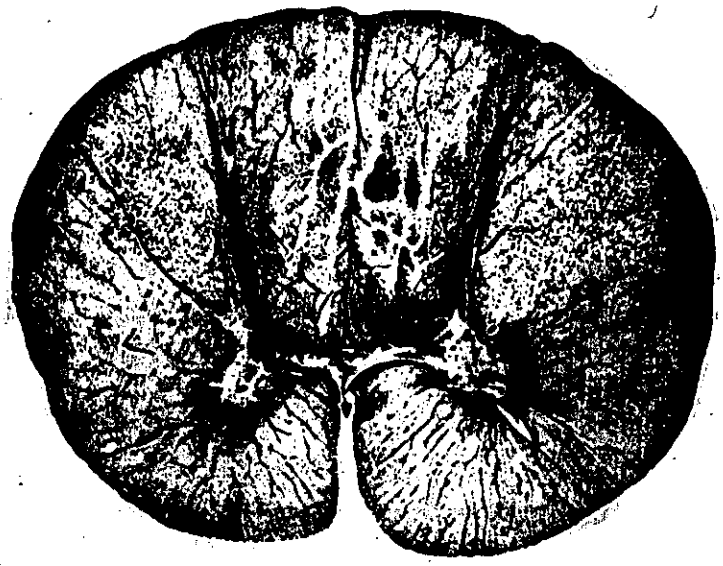

Fig. 14. Section of thoracic region of the spinal cord of a caisson worker who died on the 15th day after decompression. The dorsal and adjoining lateral columns show spongy necrosis. There appears to be rarefaction o the anterior horns of grey matter. (From LEYDEN 1878.)

ascending from a depth of 160 ft. (48 m.) where he had been for 35 minutes, lost consciousness, and upon recovery was found to be completely paraplegic. The history contained no reference to the status of sensibility. Sphincteric action was lost. Widespread decubitus developed, and death occurred *48 days* after the accident. The site of predilection of involvement was in the cervical part of the cord. Here there was rather symmetrical softening of the posterior columns (Fig. 15). The material within the affected regions consisted of detritus in which fat-filled gitter cells, axis cylinder fragments, etc., were intermixed. The interstitium of the bordering intact parenchyma was thickened by proliferated glial fibers. In the *second case*, in which the clinical history was unavailable, there were disseminated softened foci in both white and grey matter in which the reactive cells included leukocytes. There was no mention of the levels of the cord implicated, though in a general statement VON SCHROETTER remarked that the cervical and lower thoracic segments were the sites most frequently affected. The *third case*, in which death occurred *4 months* after the accident, was characterized by ascending and descending spinal cord degeneration. At the upper cervical level there was total degeneration of the fasciculus gracilis, and less pronounced degeneration of the lateral part of the fasciculus cuneatus

and of the spinocerebellar tracts. The anterior columns were unaffected. No hemorrhages were found in any of these cases.

Necrosis also characterized the changes observed in the spinal cord by SCHULTZE (1880) in the case of an 18-year-old man who became paraplegic following decompression from 4.2 atmospheres of pressure, and who died *2½ months* later. The lower one-half of the thoracic cord was affected. The posterior columns and in somewhat less measure the lateral columns showed irregular spotty lesions which on microscopic examination were found to be composed of collections of gitter cells from which the parenchyma had completely disappeared. Vessels in involved parts of the lateral columns were much thickened. Secondary degeneration of ascending tracts was evident.

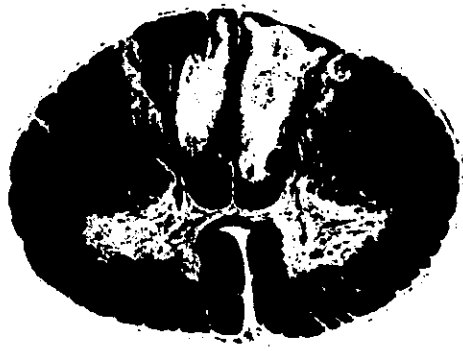

Fig. 15. Lower cervical segment of the spinal cord of a diver. There is fairly symmetrical necrosis of the posterior columns. At higher magnification of one of the necrotic foci, detritus is seen surrounded by condensed interstitium. The condensation was ascribed to glial proliferation. (From VON SCHROETTER 1904.)

SHARPLESS's (1894) report of a diver who died *2¼ months* after the onset of decompression sickness following a dive to 210 ft. (64 m.) for 15 minutes, is among the few in which lesions have been found in *spinal roots*. (Other instances have been referred to on pages 1633 and 1649.)

Upon being compressed, a diver complained of lancinating pains in his arms and legs, then lost consciousness. On recovery 1½ hours later he had severe pains in his arms and fingers. The upper and lower limbs were paralyzed. Sensibility in the upper limbs was partly preserved and below that level completely lost. There was bladder and rectal incontinence. The pains disappeared about the 53d day.

The predominant change consisted of softening of the tractus cuneatus of the cervical and uppermost thoracic segments bilaterally. Neighboring axis cylinders were greatly swollen. Severe destructive changes, not described in any detail, were noted in the adjacent part of the posterior roots. Small cavities were also found in the tractus gracilis bilaterally and in the right lateral column. Minor degenerative changes in posterior spinal roots have been noted by STETTNER (1911) in a case of divers' sickness of *62 days'* duration. The diver had been exposed to 3.4 atmospheres for 18 minutes and was decompressed over a period of 15 minutes. The brunt of the spinal cord damage was borne by the thoracic segments of the cord, especially Th 2, 3 and 4. The pathological process was limited to the white matter, in which characteristic *Lückenfelder* were seen. Only occasional excavation had occurred. An unusual feature was the extension of occasional lesions to the periphery of the cord. No evidence of hemorrhage was observed. The brain was described as free from changes.

LICHTENSTEIN and ZEITLIN's (1936) case holds the longevity record as far as post-mortem examination is concerned, the individual having died *25 years* after a bout of decompression sickness which left him paraplegic. (Actually 35 years is the record for cases observed clinically [HELLER et al., 1900].) A post-mortem study disclosed severe loss of nerve fibers with replacement gliosis in all 3 columns of the spinal cord, most extensive at middle and lower thoracic levels. In cross sections the most striking loss was midway between the grey matter and the surface of the cord. No changes were found in the brain.

Selective involvement of the *grey matter* of the spinal cord in decompression sickness seems rare. CHABAUD (1883) has reported such a case in which the patient died *30 days* following abrupt respiratory distress which developed 1 minute after decompression from more than 3 atmospheres. Motor disability in the legs and urinary and fecal incontinence persisted and muscle atrophy eventually set in, whereas the sensory deficit and the subsequent pains gradually cleared. On gross examination the softening of the cord was found to be limited to the grey matter of the lower thoracic and upper lumbar segments. A similar case was reported by GRANJON-ROZET (1880), in which the course of illness was *3 weeks*. Here, too, gross examination disclosed softening only of the grey matter in the upper lumbar and lower thoracic segments. In these 2 cases authenticity *is doubtful because of the lack of microscopic examination.*

3. Summary and comment.

In view of the many post-mortem studies in decompression sickness, both in experimental animals and human beings, it is surprising that lesions were so seldom found in the brain. In decompression to altitude, on the other hand, large lesions of an ischemic nature were the rule. We are unable to account for the difference.

By way of contrast, the spinal cord was commonly involved. In acute deaths in divers and occasionally in caisson workers, hemorrhage was frequently a conspicuous feature. It was most often epidural, but was not infrequent in the leptomeninges and subdural space. Gross hemorrhage involving the cord was most common at lower cervical levels. The greater frequency of hemorrhage in divers may be accounted for on the basis of the greater rapidity of decompression.

Perivascular petechiae in the white matter of the cord were frequent and in many of the chronic cases recounted, there was evidence of old hemorrhage. In the great majority of their animals, HELLER, MAGER and VON SCHRÖTTER found ischemic foci in the white matter unassociated with hemorrhage, from which they concluded that hemorrhages were secondary. This is an opinion now generally concurred in.

III. Clinical and pathological features of decompression to altitude.

As in caisson sickness and divers' sickness, the clinical manifestations of decompression sickness in airmen are exceedingly diverse. MASLAND (1943a) commented that, "On no single point do all cases agree. They vary from cases of sudden loss of consciousness developing with few associated symptoms, to cases in which profound circulatory collapse developed without any impairment of consciousness. In some instances, symptoms of aeroembolism were prominent,

in others they were absent. It is certain that no single disease entity can be held responsible for such a varied group of physiological disturbances." Even figures on the frequency of symptoms of a neurological nature vary, BROWN et al. (1945) having cited an incidence of 0.28%, and FERRIS et al. (1951), from 2 to 5%. BENZINGER (1941) struck a clear note when he remarked that the neurological picture in decompression to altitude is that of disseminated focal CNS damage without any clear sites of predilection.

A. Syndromes.

1. Early circulatory collapse ("primary shock") as a prominent feature.

While at altitude the subject may experience bends, chokes, etc. He becomes pale, faint, giddy, and nauseated, and breaks into a sweat. The pulse is slow, but may at first be unobtainable; it may remain slow for as long as 24 hours. The blood pressure falls transiently. Temporary visual impairment is common (GRULEE 1942). In SPROULL's (1951) 30 cases of circulatory collapse, preliminary pains were present in 60%, and in ADLER's (1950) analysis of many cases, the incidence of prior pains, chokes and abdominal symptoms, in various combinations, was 89%. Serious shock reaction, which may be fatal, is about 5 times more frequent after the development of chokes than of bends (MASLAND 1943b).

2. Delayed circulatory collapse ("secondary shock") as a characteristic feature.

Bends and chokes and other symptoms of decompression sickness, including circulatory collapse (primary shock), occur while the patient is at altitude. In some cases the collapse subsides on descent, only to recur within an hour or two, while in others the episode in the chamber is minor and circulatory collapse develops after a relatively symptom-free interval. A symptom-free interval as long as 5 hours has been reported (MASLAND 1943b). In rare instances the subject experiences no ill effects at altitude, but on reaching ground level he lapses into primary shock (slow pulse, etc.), and then, after a period of improvement, into secondary shock (rapid pulse, etc.). Primary shock may occasionally be succeeded rapidly by secondary shock while the subject is still at altitude.

Circulatory failure, pulmonary edema and pronounced hemoconcentration are characteristic features of delayed shock and in nonfatal cases may persist for as long as 24 hours. Consciousness may be retained despite profound shock, but is lost when the systolic pressure falls below 60 mm. Hg. Sometimes unconsciousness ensues even though the subject is recumbent, and under such circumstances clonic convulsive movements are not unusual.

Neurological signs and symptoms highlighting the delayed reaction are illustrated in the report of the case which follows:

A 20-year-old subject complained of bends and chokes after being at a simulated altitude of 38,000 ft. (11, 580 m.) for 18 minutes. Scintillating scotomas occurred during descent and for a time at ground level, and then, after 1¾ hours, severe headache, nausea and vomiting, and scotomas developed. At that time the blood pressure was 102/50 mm. Hg. Visual acuity became reduced, conjugate ocular movements impaired, and weakness together with increased deep reflexes and a positive Babinski sign were noted in the right lower limb. Headache became severe and stupor supervened. By 36 hours the patient was more alert and the headache less severe, and by 48 hours the visual disturbance had been reduced to a left homonymous hemianopia. By the 5th day all neurological signs had disappeared except for slightly exaggerated right knee and ankle reflexes. CSF examination 12 hours after decompression: pressure 100 mm. H_2O, total proteins 65 mg.%, sugar 85 mg.%, cell count normal (LUND, LAWRENCE and LAWRENCE 1946).

3. Focal CNS involvement as a conspicuous feature.

Symptoms of focal CNS involvement may develop at altitude or during descent, but more often appear during the first 30 minutes after descent. The latency, which may be as long as 12 hours (MASLAND 1943b), varies with extrinsic factors, being shorter the higher the altitude reached, the more rapid the ascent, and the more the subject has exercised (BROWN et al. 1945; FERRIS et al. 1943, 1944; MACKLIN 1937; ROMANO et al. 1943; STEWART et al. 1953). Although often accompanied by primary or secondary shock, the CNS symptomatology and the shock run independent courses. Thus, in the 46 cases of focal CSN symptoms reported by ENGEL et al. (1944), primary or secondary shock occurred in only 17. MASLAND (1943b) has remarked that "cases with neurological symptoms are dangerous because of the frequency of delayed circulatory collapse and the frequent occurrence of delayed neurological reactions."

An illustrative case follows:

The subject became dyspneic and had symptoms of impending collapse while at simulated altitude. On reaching ground level he was belligerent. Some 15 hours later he was disoriented and had aphasia, agraphia, right facial weakness (pyramidal type), weakness of the right arm and leg with reduction of deep reflexes, and complete right homonymous hemianopia. The hematocrit value was 60 vol.%. A transfusion of plasma was given. By the 5th day the neurological abnormalities had disappeared, and by the 9th, the patient was asymptomatic and was discharged from hospital. During the ensuing 3 months the lower part of the right side of his face was weak and he had persistent tremor of the right upper limb, intensified by activity and fatigue (GOGGIO and HOUCK 1945).

Predilection of involvement of the *spinal cord* as in caisson sickness is rare. MASLAND (1943b) has drawn attention to a few cases in which paraplegia was fleeting, and BOOTHBY and LOVELACE (1938) reported an instance in which paralysis from the waist downward developed during exposure to a simulated altitude of 35,000 ft. (10,670 m.), but disappeared by the time that ground level was reached. The only case of chronic spinal cord involvement in man has been reported by DÖBELN and HÖÖK (1954). (This case has been referred to in detail by HAYMAKER and JOHNSTON 1955.) The patient, a 36-year-old, moderately obese pilot, ascended to a simulated altitude of 36,000 ft. (11,000 m.), and at that level complained of abdominal distension. The ascent was continued to 39,400 ft. (12,000 m.) and during the ascent the abdominal pain became worse. Sensations of numbness developed in the ulnar area of both hands. A few minutes later the test-run was interrupted. At ground level the patient soon lapsed into severe shock, and he was found to have complete flaccid quadriplegia. The shock was successfully countered, but the flaccid quadriplegia persisted. Gradual improvement set in so that 7 months later the patient was able to leave the hospital without support. During the entire course, the limb muscles were flaccid, not spastic. Moderate atrophy persisted in the gastrocnemius and soleus muscles of one leg, which is of interest in view of the observation that in hypoxidosis of the spinal cord the more central part of the anterior horn, supplying gravity muscles, is affected, and the peripheral part, suppliyng antigravity muscles, is spared (KROGH 1950). No sensory disturbance was reported. The account resembles that in the case of a caisson worker reported by CHABAUD (p. 1642).

Cases with CNS involvement are fairly common. The EKG disturbances include sinus tachycardia, sinus bradycardia, sinus arrhythmia and premature ventricular beats, auricular extrasystoles, and right axis deviation (ADLER 1950).

4. Disturbances of cardiac origin as an outstanding feature.

The foregoing *classification* is an adaptation of one proposed by MASLAND (1943a & b). Taking into consideration the overlap of circulatory and neural symptoms in decompression sickness, ADLER (1950) suggested classifying cases

as 1. chiefly neurological, 2. chiefly circulatory, and 3. neurocirculatory. He pointed out that of an estimated 1,000,000 men exposed to decompression to a simulated 30,000 ft. (9,140 m.) or above there have been 400 cases of collapse (0.04%), of which 150 were regarded as serious. In an analysis of 314 of the cases, he included 24 in his classification *1*, 23 in *2*, and 267 in *3*.

Reference should be made to *visual disturbances* and *migraine-like headache* because of their frequency. As a rule, each is heralded by bends, chokes, etc. (BLANKENHORN and FERRIS 1944; ENGEL et al. 1944, 1945; FERRIS et al. 1951; WHITTEN 1946). *EEG wave changes* have been noted as long as neurological abnormalities persist, but there has been no EEG evidence of lasting changes in the cerebrum (ENGEL et al. 1943b, 1944). Worthy of emphasis with respect to *abnormal reflexes* is that they may shift from one side to the other before they become stationary (ADLER 1950). *Tremor, adiadochokinesis* and a *hand-writing disorder* resembling that in extrapyramidal motor disorders have also been observed (BENZINGER 1941).

B. Clinical and laboratory data in cases in which shock prevailed.

In his analysis of several cases of collapse due to decompression, 6 of them fatal, ADLER (1950) noted that hemoconcentration was the rule, with the hematocrit rising as high as 70 vol.% (usually 50 to 55 vol.%), erythrocytes to 8.1 million (usually 5.5 million), and hemoglobin to 134% of normal (usually 100% or slightly more). Leukocytes were disproportionately high as compared to the degree of hemoconcentration, being as high as 57,450 per cmm. Blood sludging has not been found in airmen decompressed to altitude (KNISELY 1943).

The following cases are illustrative of shock in the absence of recognized focal CNS manifestations.

Case 1 of COTES (1953). An obese man (184 lb., 5′ 7″), aged 29, had been at a simulated altitude of 37,000 ft. (11,275 m.) for 6 minutes when he complained of bends, chokes, and abdominal cramps. Mild primary shock then developed. On reaching ground level he was much improved; BP 130/80; pulse rate (P) 108. *70 minutes later:* frontal headache, secondary shock (BP 130/80), urine normal. *Next 3 hours:* received O_2; BP 130/80. *5th hour:* shock persisted (T 95.4° F., BP 135/80, P 96, R 23); scattered rales in chest; nystagmus. EKG: in lead 3 the P-wave was sometimes inverted and the T-wave constantly inverted, which "suggested a disturbance of the heart without any definite localization." Blood examinations on admission, 3 hours and 4 days after collapse: Hb. 121, 122 and 106%; hematocrit 60, 60 and 48 vol.%. *Day after onset:* condition improved though cyanosis persisted; roentgenograms showed considerable resolution of pulmonary edema. *Week after onset:* well.

Case 2 of COTES (1953). A man aged 37, of average build (126 lb., 5′ 7″), became drowsy and pale after being at a simulated 37,000 ft. (11,275 m.) for 10 minutes. At the end of 24 minutes he had bends, and 10 minutes later became unconscious. On descent to 18,000 ft. (5,500 m.) he recovered consciousness and vomited. At ground level, BP 100/60, P 72; given O_2. *50 minutes after collapse:* BP 120/75, P 64, still in shock. *2 hours, 10 minutes:* BP 115/75. *3 hours, 10 minutes:* asymptomatic, BP 150/80, P 80, R 23, moderate pulmonary edema, EKG normal. Hematological examination $2^1/_2$ hours and 24 hours after collapse: Hb. 109 and 104%, hematocrit 51 and 45 vol.%. *5 days after collapse:* well.

C. Symptomatology, laboratory data and visceral changes in fatal cases.

1. Symptomatology and laboratory data.

The symptomatology of 12 fatal cases is given in Table 1 (p. 1614). While at altitude, 10 of the patients were known to have had one or more manifestations of decompression sickness (e.g., abdominal pains), all had symptoms of primary shock, and 5 of these had paresis of limb and/or extraocular muscles. Upon reaching ground level, 4 of the patients were relatively symptom-free for periods

up to 45 minutes. Secondary shock supervened and dominated the clinical picture and proved irreversible. In 2 cases chokes recurred. Paresis or paralysis or reflex changes were noted in 7. Blood pressures when first taken varied, in some cases being low and in others temporarily elevated (Table 2; p. 1616).

Steadily increasing hemoconcentration was a feature in all cases in which such data are available, except for Case 4, in which the concentration returned toward normal (Table 2). In Case 1 there was also hemoconcentration, for at autopsy the heart was filled with dark blood having the consistency of "very thick syrup." In Case 9 (as also in COTES's Cases 1 and 2 [p. 1645]), the electrolyte and other changes were those characteristic of heart failure. COTES (1953) estimated that in Case 9, some 3 liters of fluid were lost from the circulation during the first $2^1/_2$ hours after collapse, through passage, presumably, into the subcutaneous tissues and intestines.

2. Visceral changes.

Study of the thoracic and abdominal viscera served to confirm the occurrence of acute circulatory failure in all cases (Table 2). Vascular engorgement was noted in most of the viscera. Occasional fragmentation or acute retrogressive change in cardiac muscle fibers was observed in about half the cases. (Further data on the status of the heart are given on pages 1652 and 1657.) The lungs were characterized by striking vascular congestion together with intra-alveolar edema fluid. Intravacuolar inclusion bodies in hepatic cells were noted in 2 cases, a change previously observed in decompressed experimental animals (TROWELL 1943). No focal necrosis of hepatic cells was seen. Scattered heme casts or frank lower nephron nephrosis were found in 5 cases (Cases 4, 5, 7, 11 and 12), as has been noted previously (FERRIS et al. 1951; GOGGIO and HOUCK 1945; HAYMAKER and DAVISON 1950; MASLAND 1944). In most of these 5 cases there was associated tubular degeneration of the adrenal cortex. Occasional small splenic infarcts were found in 1 case (Case 11). Changes in the gastrointestinal tract consisted of striking edema of the ileum (Case 2), widespread hemorrhage into the jejunum and ileum (Case 3), acute ulceration of the stomach with hemorrhage (the largest ulcer 2 cm. in diameter) (Case 11), and perforation of the stomach with discharge of about 300 cc. of the gastric contents through the necrotized diaphragm into the left pleural space (Case 7). The bone marrow contained tiny hemorrhages in 2 cases (Cases 1 and 7). Fat stains of the liver and adrenal cortex showed a higher lipid content than in the usual run of autopsy cases.

An observation of considerable interest in 6 of our 9 fatal cases was the presence of fat emboli in vessels of the lung, some of which were doubly refractile: the emboli were fairly numerous in 3 (Cases 2, 5 and 12) and relatively few in the other 3 (Cases 1, 4 and 6). In the seventh case a few fat emboli were seen in an intrarenal artery (Case 11), and in the eighth and ninth (Cases 3 and 7) there was an occasional fat embolus in the brain. Fat emboli in the brain, always very sparse, were found in Cases 3, 7 and 12.

D. CNS pathological changes.

1. Spinal cord.

The only instance of our group in which the entire spinal cord was available for study was Case 3 (Tables 1 and 2).

This patient was among the oldest of the group (38 years) and very obese. On reaching a simulated altitude of 30,000 ft. (9,140 m.), he complained of sharp pains in both knees,

When, after 1 hour at this height, he ascended to 38,000 feet (11,580 m.) widespread pains and a choking sensation forced him to abandon the flight. At ground level he felt prostrated, was sweating profusely, had diplopia, and his right arm was weak and paresthetic. After 45 minutes the *neurological disorders disappeared*, but a *feeling of generalized weakness* remained.

On admission to hospital $1^1/_2$ hours after the onset of symptoms the patient was in moderately severe secondary shock. He was well oriented. Neurological examination was said

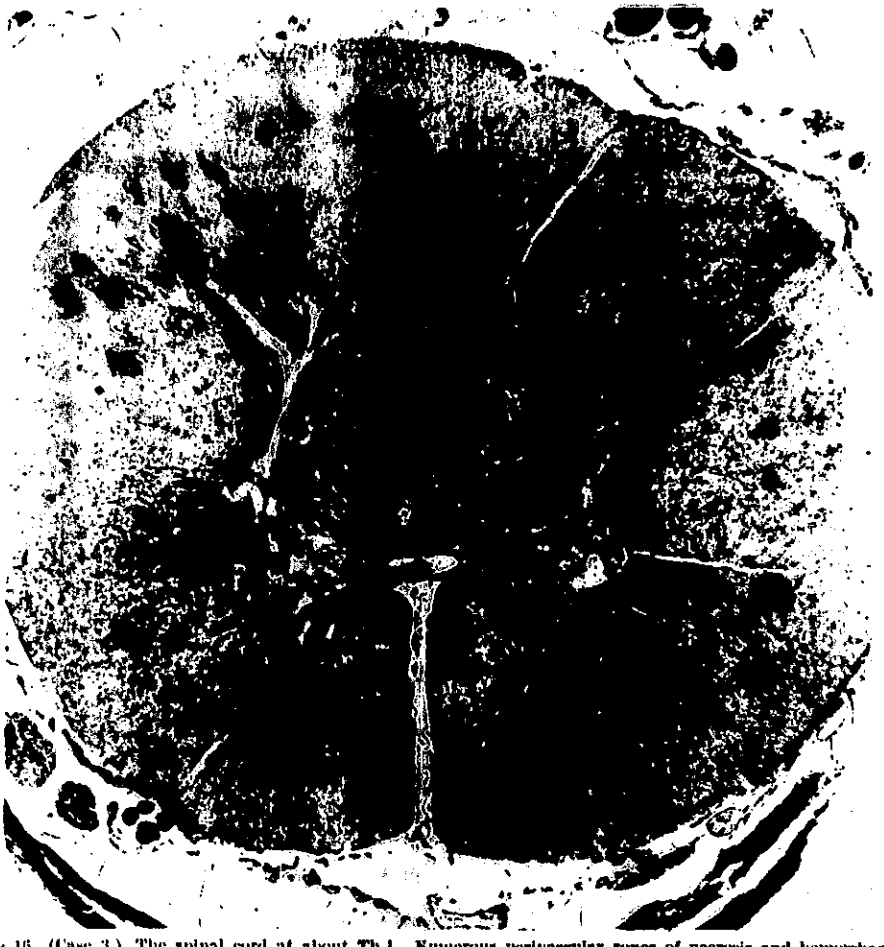

Fig. 16. (Case 3.) The spinal cord at about Th 1. Numerous perivascular zones of necrosis and hemorrhage are present in the white matter, and parenchymal disruptions in the grey. The darkened zones about some of the hemorrhages and at the edge of the grey matter probably represent plasma transudate. The anterior spinal and radicular arteries are empty, whereas the meningeal and radicular veins are engorged. MALLORY phosphotungstic acid hematoxylin stain. (*From* HAYMAKER *and* DAVISON *1950.*)

to be negative. O_2 therapy was begun. With shock deepening some 5 hours later, the patient was given 500 cc. of plasma, and an hour later another 500 cc. At 14 hours after onset the patient, although in deep shock, was still able to answer questions coherently. Two hours later he was much weaker, very restless, complained of pains in the wrists, and was cyanotic despite being in an O_2 tent. Consciousness persisted until a few minutes before death, which occurred $17^1/_2$ hours after decompression.

At lower cervical and upper thoracic levels of the spinal cord there were many perivascular lesions in the posterior and lateral columns of white matter (Fig. 16), consisting of perivascular parenchymal necrosis into which hemorrhage had occurred. The grey matter at these levels, particularly in the region of

the junction of the anterior and posterior horns, was characterized by disruptions in which occasional erythrocytes were scattered (Fig. 17A). Nerve cells in such foci had undergone severe regressive changes. In smaller foci in the grey matter, the parenchymal disruptions were perivascular in location. A conspicuous feature of such foci was that of a ballooning of nerve fibers: in cross section the fibers had the appearance of large ruptured ringlets (Fig. 17B). Plasma had infiltrated into the white matter (Fig. 18A), and in some foci, oxis cylinders were unstained

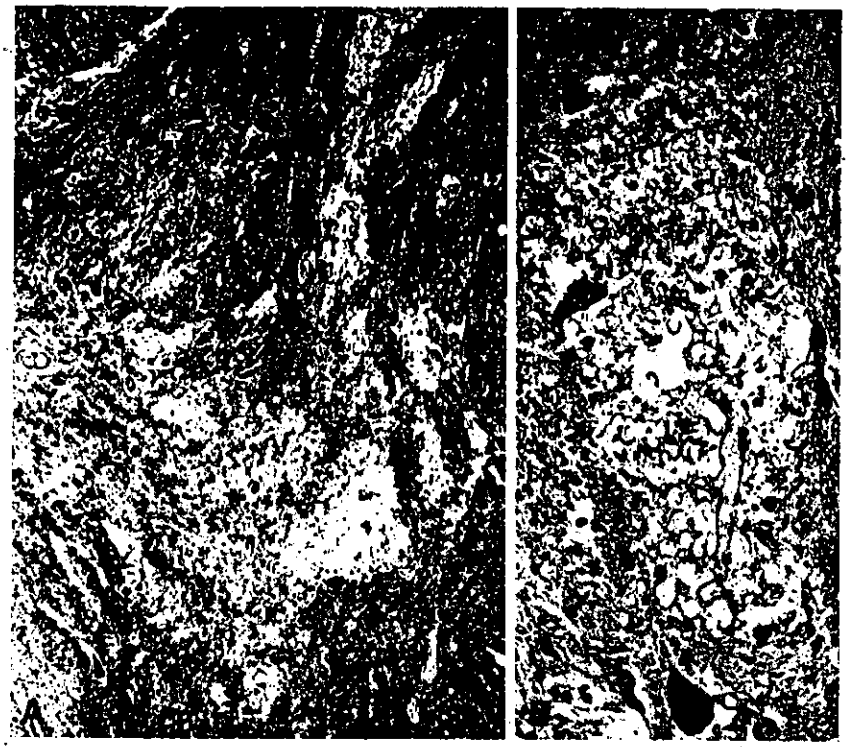

Fig. 17A and B. A (Case 3). Enlarged view of the grey matter illustrated on the right side in Fig. 16. There are numerous tissue gaps, some of which are perivascular. Nerve cells in such areas are exceedingly pyknotic. The deeper staining of white matter adjacent to the grey is due apparently to the infiltration of plasma into the interstitium. MALLORY phosphotungstic acid hematoxylin stain. B (Case 3). Perivascular parenchymal focus in the grey matter showing numerous large vacuolar structures. These are ballooned nerve fibers. Some have ruptured. The central vessel is engorged with blood. No hemorrhage is visible. Hematoxylin-eosin stain.

(Fig. 18B). Myelin sheaths in such regions showed the fenestration, etc. typical of degeneration. No vascular thrombi were noted.

In another case (Case 2), in which the uppermost cervical cord was available, minute to moderate-sized foci of the same disruptive character were found in the grey matter. In still another (Case 1), disruptive parenchymal changes were found perivascularly in the medulla oblongata, but there was no ballooning of the implicated nerve fibers.

In a third instance (Case 12) only the uppermost cervical part of the cord was available for study. In the anterior horns there was massive disruption, some of which might be accounted for on the basis of artefact. However, in the posterior horns there were clear-cut perivascular foci of parenchymal sponginess in which nerve fibers were greatly enlarged, as in Figure 17B. A few foci of this kind were found also in the white matter, which otherwise appeared unaffected (HAYMAKER, JOHNSTON and DOWNEY 1955).

2. Spinal roots and cranial nerves.

In 5 cases, vacuolization of the myelin sheath of roots and nerves was noted, but no interpretation could be made as to its meaning. In 1 case (Case 11) the root of the facial nerve contained several round vacuoles having a diameter of about 2 to 5 times that of a nerve fiber. The vacuoles centered in the endoneurium, widely separating the nerve fibers. In sections stained by routine methods no nuclei characteristic of those of fat cells were seen. No fat stains were performed. The vacuoles, which are discussed elsewhere (HAYMAKER, JOHNSTON and DOWNEY 1955), might possibly represent the spaces left by previously existing gas bubbles.

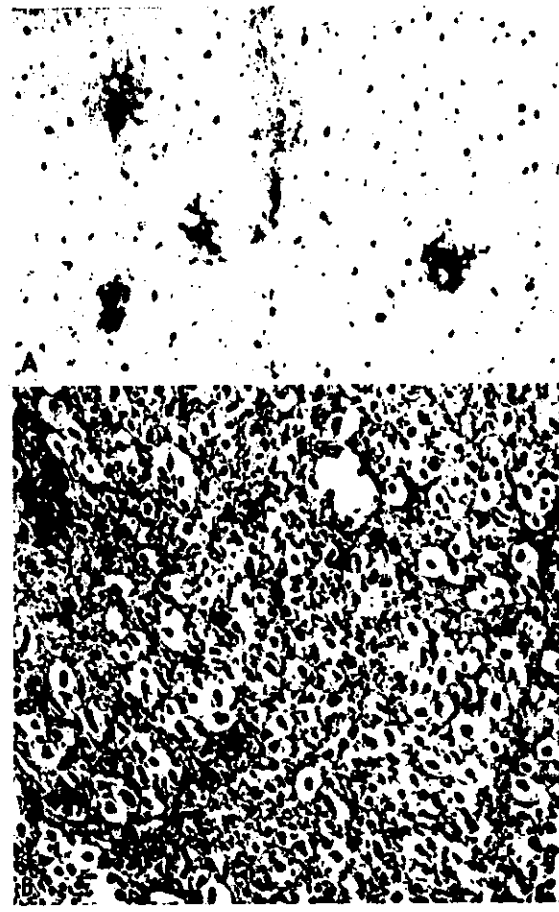

Fig. 18 A and B. (Case 3.) Plasma transudate in white matter. A. Posterior columns, showing 4 vessels from which plasma has extended into the parenchyma. The elongated vertical structure is the posterior median septum of the cord. Thionin stain. B. The nerve fibers have been widely separated by the plasma transudate. A few axis cylinders to the left are disrupted or swollen and some are not visible. The pool of plasma to the right seems to have come from the superjacent vessel. BODIAN activated protargol method.

3. Leptomeninges and brain.

Venous and capillary engorgement was the only significant change in the leptomeninges except for trabecular macrophage activation in 2 cases in which erythrocytes were present in the arachnoid meshes (Cases 2 and 3). Sponginess was noted in subpial parenchyma in most of the cases, and in the upper cortical laminae and the floor of the IVth ventricle in one case each. Frequently the vessels of the cortex at the depth of cerebral sulci were empty, while those elsewhere along the sulci and over the crest of the gyri were engorged with blood. Slight laminar (lamina III) and focal ischemic nerve cell changes were occasionally noted in the cortex at the base of sulci, but were exceedingly sparse elsewhere in the cortex except for SOMMER's sector of the hippocampus, which exhibited ischemic nerve cell changes which increased in severity with time. PURKINJE cells of the cerebellum remained virtually unaltered.

By way of contrast, there were changes in the white matter in all cases, but they varied greatly in degree. Cases 1, 2 and 4 (8 hr., 17 hr., and 2 days and 7½ hr. in duration respectively) were characterized by spotty, perivascular edema, with rather slight myelin changes in the edematous foci. On the other

hand, in Cases 3 and 5 ($17^1/_2$ hr. and 3 days, 10 hr. duration) the changes were pronounced, and consisted of perivascular areas of striking parenchymal pallor, sponginess, with individual foci often confluent (Fig. 19). Axis cylinders in the involved areas were spared. Astrocytes presumably undergoing activation were well brought out by the HOLZER glia fiber stain in 3 cases (Cases 1, 2 and 3). Caudate nucleus, thalamus and pars basilaris pontis exhibited occasional peri-

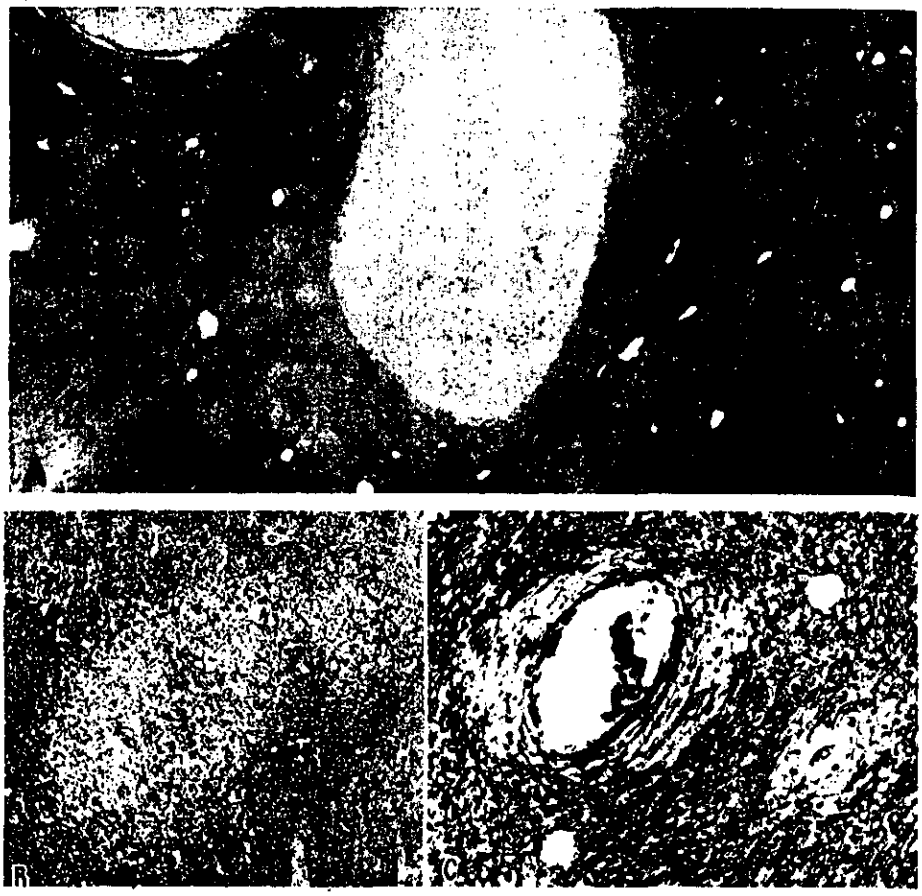

Fig. 19A–C. Ischmic foci in white matter. A (Case 3) illustrates myelin rarefaction of the subcortical white matter, chiefly perivascular. WEIL myelin stain. In B (Case 5), from the subcortical white matter, there is severe parenchymal sponginess. Oil-red-O stain. C (Case 1), from the cerebellar white matter, showing perivascular parenchymal rarefaction. MALLORY phosphotungstic acid hematoxylin stain.
(From HAYMAKER and DAVISON 1950.)

vascular collections of lymphocytes (Fig. 20), and scattered nerve cells of the striatum and pallidum in particular had undergone regressive changes. Now and then, condensed or foamy plasma transudate was found perivascularly (Fig. 21).

Sparse scattered perivascular hemorrhages were noted variously in the cortex, white matter, basal nuclei, wall of the IIId ventricle, periaqueductal region, and floor of the IVth ventricle.

Clumps of *crystalline pigmentary material* having a dark brown color were occasionally found in the blood stream, and individual pigmentary granules were seen in intravascular and extravascular erythrocytes and in the cytoplasm of nerve cells, particularly in Case 1 (Table 1; p. 1614). The pigmentary material

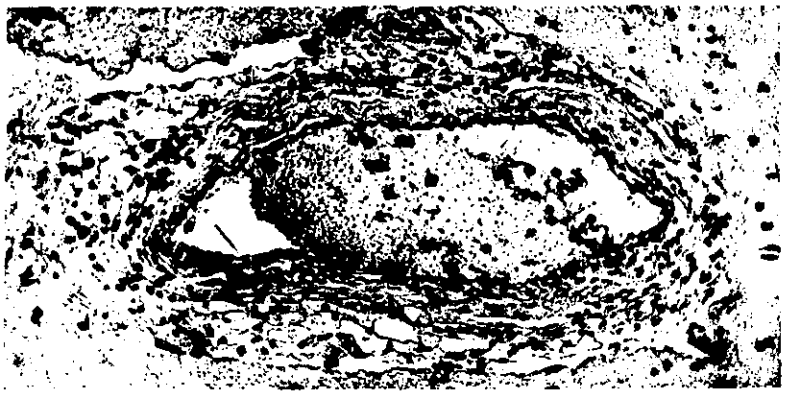

Fig. 20. (Case 2.) From the head of the caudate nucleus. Perivascular cell infiltrate. Most of the cells are *of the lymphocyte series. Others are macrophages.* Hematoxylin-eosin stain. (From HAYMAKER and DAVISON 1950.)

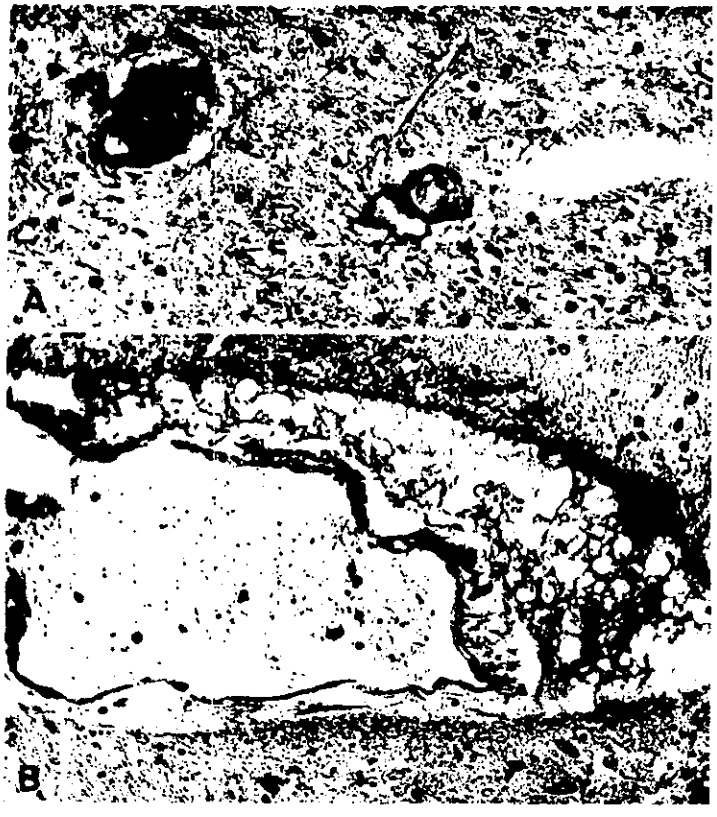

Fig. 21 A and B. (Case 1.) Perivascular accumulation of plasma: A, in the medulla oblongata, and B, in the pars basilaris pontis. The perivascular plasma in *B* has a bubble appearance. Hematoxylin-eosin stain.

was negative for iron and was shown not to be "formalin pigment." It was apparently a derivative of the non-iron-containing porphyrin ring of hemoglobin. In this connection, disintegrative changes were found in intravascular erythrocytes. The presence of the pigmentary material in nerve cells probably reflects

nerve cell damage. Pigment presumably of the same nature has been observed by others in decompression sickness and in air embolism (pp. 1633 and 1631).

Cases 11 and 12 were of particular interest because of the presence of a *patent foramen ovale* in the heart. (The significance of the patency is discussed on page 1656.) In the remaining cases no statement was available as to the patency of this foramen. The weight of the heart in Case 11 was considerably increased, suggesting that much blood had flowed through the foramen and thus taxed the heart. There were also numerous rather large areas of myocardial fibrosis in the interventricular septum. In Case 12 the heart weight was normal, and the myocardium intact. In one other case (Case 3) there was cardiac enlargement (410 Gm.), but the myocardium was normal except for fragmentation of muscle fibers and edema. Only in Case 11 and 12 were the coronary arteries significantly sclerotic, but in neither was there evidence of recent cardiac infarction (HAYMAKER, JOHNSTON and DOWNEY 1955).

Case 11. A moderately obese airman, aged 50, was flying as a passenger in a jet plane at 36,500 ft. (11,100 m.) (cabin pressure 35,500 ft., 11,000 m.) for 70 minutes when he complained of "cramps in the stomach." Some 12 minutes later he slumped forward unconscious. Upon landing 12 minutes afterward he was still unconscious. The blood pressures are given in Table 2 (p. 1616). The EKG was normal. The spinal fluid was under a pressure of 260 mm. H_2O and contained 20 erythrocytes per cmm.

On admission to hospital, the airman was comatose but withdrew from painful stimuli. B.P. 90/50, P 90. The pupils reacted to light. The muscles of all the limbs were flaccid and twitched periodically. The Babinski toe sign was positive bilaterally. Copious coffee-colored fluid was vomited. No clinical evidence of pulmonary edema was found. About 6 hours after he reached the hospital, the blood pressure was 130/? and the pulse 125 and irregular. There was tremor and jerking of the right lower limb. The pulse became progressively weaker and the respirations more shallow and gasping, and cyanosis increased. Death occurred $11^1/_2$ hours after collapse.

Post-mortem study of the viscera revealed severe congestion of the lungs, liver, spleen, and thymus. Further data are given in Table 2 and under *Visceral changes* (p. 1646). Oil-red-O stained sections disclosed intense lipemia, but only in an intrarenal artery were fat emboli observed. The heart weighed 625 gm. and was hypertrophic, its left ventricle being 18 mm. and its right ventricle 2 to 5 mm. thick. Considerable coronary sclerosis was found, without, however, a significant decrease in the size of coronary lumina. There were scattered fairly large foci of myocardial fibrosis of the interventricular septum. The foramen ovale was described as anatomically patent and sufficiently large to admit the tip of the little finger.

Grossly the brain appeared normal except for engorgement of leptomeningeal venules and capillaries. Microscopic examination revealed many small and large areas of early ischemic necrosis of the cerebral cortex of all lobes and frequently of the adjoining white matter as well (Fig. 22). Similar but smaller lesions of this kind were noted occasionally in the corona radiata and internal capsule. Many of the ischemic areas were wedge-shaped, with the base of the wedge in the white matter and the apex in the cortex. The lesions were well delimited, often confluent, and sometimes of geographical pattern. Some lesions occupied all laminae. Smaller areas of ischemic necrosis were clearly perivascular. In severely necrotized areas most of the nerve cells were extremely pyknotic and hyperchromatic, numerous myelin sheaths had disappeared or were irregularly swollen, beaded, or fenestrated or had disappeared, axis cylinders were pale or had suffered disintegrative changes or had disappeared, and many glial nuclei were faded or shrunken. Astrocytes at the periphery of some of the foci appeared to be in a reactive state. Furthermore, the walls of occasional small venules

displayed evidence of necrosis, and now and then scanty collections of lymphocytes were noted perivascularly. The ischemic areas were loculated, and their borders very spongy, and now and then a homogeneous material, presumably clotted edema fluid, was found in the interstices of ischemic areas. A few lymphocytes and macrophages were seen in the perivascular spaces of some of the involved areas. Small perivascular petechiae were scattered in the brain stem and in the grey and the white matter of the cerebrum.

The cortical nerve cells in areas free from the ischemic lesions appeared normal. The cells of the hippocampal formation were also spared. Pallidum, thalamus, midbrain nuclei and other cerebral nuclear masses were virtually free from change. In the putamen, superior colliculus and pars basilaris pontis, sizeable ischemic foci were observed, but they were very few. The medulla oblongata appeared normal, as did also the uppermost spinal cord. The remainder of the cord was not available for study. Areas of ischemic necrosis precisely the same as in the cerebral cortex were scattered through the cerebellum; they were relatively large and involved the molecular, granular and PURKINJE cell layers. (They were identical with those illustrated in Fig. 26.) Foci of this kind were also noted in the cerebellar white matter. Rather abundant erythrocytes were found in the cerebellar leptomeninges in a few areas.

Fig. 22. (Case 11.) Large and small areas of ischemic necrosis in cortex and subcortical white matter. The ischemic areas, some of geographical pattern, have a clear-cut border in which the parenchyma is spongy. LILLIE myelin stain.

Case 12. An obese individual, aged 34 years, was flying as a passenger in a jet plane at an altitude of 35,000 ft. (10,670 m.) (cabin pressure 26,000 ft., 7,900 m.) for 1 hour and 40 minutes, and on ascending to 38,500 ft. (12,040 m.) (cabin pressure 29,000 ft., 8,840 m.), he complained of numbness of the left side. Shortly afterward he lost consciousness. When the plane landed 20 minutes later, he was semicomatose and was thrashing about so that restraint was required. B.P. 180/120, then 130/90; P 130. The left limbs were motionless and flaccid. The plantar reflexes were flexor. Subsequent examination confirmed these observations and revealed an absence of superficial abdominal and cremasteric reflexes and a reduction in tonus of the right arm and leg. Frothy fluid was being expelled from the respiratory tract. Death occurred 6 hours after the onset of symptoms.

At autopsy the brain and the abdominal and thoracic viscera were removed under water. No gas bubbles were found. The lungs were congested and edematous. The heart weighed 380 gm. and its walls were of normal thickness. A few subendocardial hemorrhages were noted, the largest, 1.5 cm. in diameter, being

Fig. 23 A and B. (Case 12.) Patent foramen ovale. A illustrates the foramen as seen on the left side of the interauricular septum, and B the right side.

in the superior aspect of the interventricular septum. Examination of the coronary arteries revealed an atheromatous plaque of the left circumflex branch at the first bifurcation, occluding about 60% of the coronary lumen in that region.

Fig. 24. (Case 12.) Fat emboli in lung. Oil-red-O stain.*

A patent foramen ovale had the form of a canal, 4 mm. high and 1.5 mm. wide, which traversed the interauricular septum tangentially, issuing on the right side into an opening 6 × 4 mm. in diameter, and on the left 16 × 4 mm. (Fig. 23). Much pancreatic tissue was replaced by yellow fat. Of especial interest microscopically was the presence of numerous fat emboli in the lungs (Fig. 24). They were visible in 16 of the 18 sections of the lungs. A few were also found in the brain, where they had not elicited any reaction.

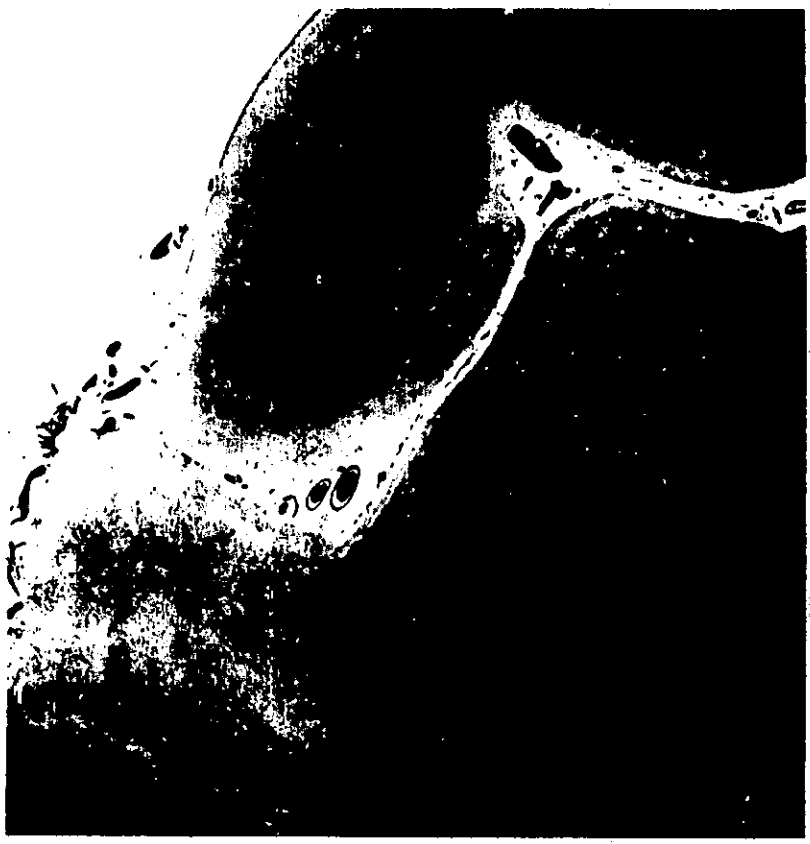

Fig. 25. (Case 12.) Island of REIL and operculum, showing myriad perivascular ischemic foci in the cortex and larger foci involving both cortex and white matter. LILLIE myelin stain.

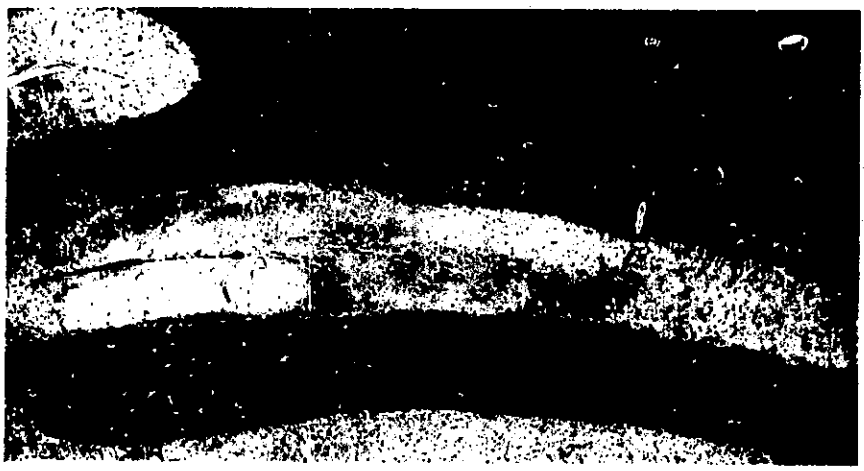

Fig. 26. (Case 12.) Cerebellum, showing numerous areas of early ischemic change in the molecular, PURKINJE and granular layers. LILLIE myelin stain.

Examination of the gross brain showed little of significance aside from capillary engorgement, mainly over the convex surface of the cerebrum. Microscopically there were many ischemic lesions of the same character, number and distribution as in Case 11. The lesions were found in all lobes of the cerebrum. Myriad small perivascular ischemic foci predominated in some regions (Fig. 25). Nerve cells and myelin within the ischemic areas had suffered profoundly. Perivascular petechiae were noted now and then, especially within ischemic areas. Cellular infiltrates were absent. The nerve cells of the hippocampal formation appeared unaffected. Deeper structures of the brain in which ischemic foci were observed were the septum pellucidum, anterior commissure, head of the caudate nucleus, and pars basilaris pontis. Numerous ischemic areas were found in the cerebellum (Fig. 26), and within such areas as well as in the overlying meninges there were occasional perivascular petechiae. Conspicuous perivascular hemorrhages were seen in the floor of the IVth ventricle at the mid-pontile level.

The brain changes in all cases listed in Table 1 (pp. 1614 and 1615) have been discussed except for Case 7. This case proved an exception from the pathological standpoint in that the cerebral cortex and adjoining white matter contained many large ischemic foci identical with those in Cases 11 and 12. In addition, the cortical newe cells at the base of many sulci exhibited advanced necrosis. The cerebellum failed to show any conspicuous change. No laminar change was seen in the cerebral cortex, and the hippocampus appeared normal. Slight perivascular edema was to be seen here and there in the cerebral white matter. There was no record of the status of the foramen ovale, but an eye-witness stated some 5 years later that it was closed.

4. Summary and comment.

Many of the changes in the thoracic and abdominal viscera were characteristic of those seen in circulatory collapse, even to the presence of heme casts in renal tubules (lower nephron nephrosis). An impressive feature was the presence of fat emboli in all 9 cases, though they were few in 6. Pulmonary fat emboli have been found post mortem in individuals who died from severe chronic disease unrelated to trauma (WARTHIN 1913), and they have been noted in "normal" animals (MCKIBBEN 1919; PELTIER 1954). Whether they were a factor in the fatal outcome or whether they are only of academic interest is a moot point. As postulated previously (HAYMAKER and DAVISON 1950), bone marrow may be the site of origin of the fat emboli, for it contains blood sinusoids with relatively rigid walls which, if ruptured by accumulating gas, would allow fat to be aspirated into the blood stream. If this interpretation is correct, it would follow that other products of disintegrated fat cells have been delivered into the blood stream, e.g., potassium ions and histamine-like substances. It is suggested that, as in fat embolism due to any other cause, such products may so act on vessel walls that circulatory stasis, then shock, ensues. This is in line with the hypothesis of the causation of decompression sickness proposed by FERRIS et al. and by MASLAND (p. 1613), but we believe that decompression sickness is due not only to the presence of circulating tissue constituents but also to N_2 bubble embolization. Fat emboli were more numerous in a case of divers' sickness (Case 13) (p. 1630) than in any of the cases of decompression to altitude. This is of especial interest in view of the fact that, all other factors being equal, much more N_2 is liberated from the fat tissues in decompression from increased atmospheric pressures than in decompression to altitude.

With reference to the lesions in the brain, the cases are divisible into two groups, the decompression-chamber cases and the jet-plane cases. In the decompression-chamber cases the lesions were, for the most part, confined to the cerebral white matter. Reduction in O_2 tension in connection with the severe shock, as a result of which perivascular edema readily develops in the brain (SCHNEIDER 1953; SCHOLZ 1949), could be held partly responsible for these lesions. However, in our opinion, the lesions in two of the cases at least (Cases 3 and 5; Fig. 19) developed too early and were too severe to be accounted for on the basis of fall of blood O_2 tension alone. It is postulated, therefore, that the lesions in the white matter were due in part to the lodgement of N_2 bubble emboli. The emboli would necessarily have to be tiny and their total volume small in order to reach the white matter without halting in vessels of the cortex. In this connection, it has been shown that tiny paraffin emboli may induce lesions exclusively in the white matter, and larger emboli, predominantly in the cerebral cortex (SWANK and HAIN 1952).

As to the 2 jet-plane cases in which the foramen ovale was patent, the lesions in the brain were identical with those observed in air embolism. In these cases it seems logical to assume that N_2 bubbles arising in peripheral tissues and venules were transported to the right auricle, thence to the left auricle (the pressures in the 2 auricles being virtually the same), and then to the brain. Vasoconstriction in cortical vascular beds due to ischemia from the lodgement of N_2 bubbles plus reduction in blood O_2 may have been still another factor in the development of the cortical lesions. The changes in the brain in Case 7 (p. 1656), very similar to those in the 2 jet-plane cases, are not easy to explain. We can probably rely on the statement that the foramen ovale was closed. In view of the rapidity and severity of the ischemic changes, it seems necessary to assume that N_2 bubble embolization was a factor in their production.

Multiple ischemic foci in the spinal cord duplicated those observed in caisson and diver's sickness. There was, however, a difference in that in decompression to altitude the grey matter, i.e., the anterior horns, were predominantly affected (Cases 3 and 12). This difference is not very sharp, for grey matter of the cord may also be affected in caisson and in diver's sickness, as illustrated in Figure 14. If capillary density of the spinal cord were the only factor concerned, the white matter should always be the site of predilection. But since, in some cases, the grey matter *is* the site of predilection, it seems logical to conclude that an additional pathogenic factor is spinal arterial or arteriolar spasm brought about by the intra-arterial collection of N_2 bubbles. More specifically, we refer to the sulcocommissural arteries, which are, practically speaking, end-arteries. Under such conditions the white matter may be comparatively spared owing, presumably, to the richness of the anastomoses of the arteriae coronae. The question of whether autochthonous bubble formation is a factor in the causation of the lesions in the white matter is still an open one.

One further factor in the production of spinal cord lesions is to be considered. N_2 bubbles from retroperitoneal fat may gain the spinovertebral-azygos system of veins, and through obstructive action retard venous return from the cord and thus facilitate embolization of spinal arterioles and precapillaries. Under extreme conditions, engorgement of this venous system may be aggravated through back-pressure from bubble-laden pulmonary vessels.

In conclusion, the production of embolic lesions in the cord seems to be as dependent on retardation of blood flow on the venous side as on the arteriolar-capillary side.

IV. Primary decompression phenomena in diving operations and in explosive decompression to altitude.

A. Primary decompression phenomena in divers.

The most serious primary decompression phenomena in divers are those due to overdistention of the lungs. Overdistention may be brought about, for example, when a diver using a MOMSEN "lung" holds his breath during ascent until the intrapulmonic pressure becomes 60 mm. Hg higher than the hydrostatic pressure. In a particular case recounted by POLAK and ADAMS (1932) and by BEHNKE (1932), the diver rose from a depth of 15 ft. (4.6 m.) at the conventional rate, swam to the ladder of the float, started to climb up, but fell backward into the water. On being rescued he breathed a few times and died. Post-mortem examination revealed dilatation of the right ventricle of the heart, numerous petechiae throughout both lungs, minute tears in the parietal pleura, and a small subarachnoid hemorrhage over the parietal area of the brain. In another fatal case, described by POLAK et al. (1930), the individual, using a MOMSEN "lung," rose from 30 ft. (9.2 m.) and collapsed on ascending the ladder to the float. Post-mortem study revealed bloody mucus in the bronchi and widespread elevation of the visceral pleura by air bubbles which varied from 1 to 10 mm. in diameter. On compression of the base of the heart, air bubbles could be felt passing into the aorta.

Two further fatal accidents during practice runs in a diving tank have been reported by KINSEY (1954). Death occurred shortly after ascent. There was emphysema of the lungs and mediastinum in one and probably in the lungs in the other. Air bubbles were found in the leptomeningeal vessels in both instances, but the significance of this observation is open to question since the brain was not removed under water. In one of these cases, air was also found in the right auricle and ventricle, which led KINSEY to conclude that death was due to stagnant (ischemic) hypoxia related to the entrapment of air in the heart.

Another fatal instance has been reported by SCHERSTÉN (1948), as follows:

A diver was lowered into a tank to a depth of 66 ft. (20 m.), then rose normally to 33 ft. (10 m.), at which time the O_2 cock to his nose piece was accidentally turned off. He reached the surface 5 seconds later, swam to the edge of the pool, and then lost consciousness. Initially he was not cyanotic. Death occurred in 42 hours.

The pulmonary air sacs were found to be enlarged and probably ruptured, vessels were engorged with blood, and the alveolar septa contained hemorrhages. Sharply demarcated large and small foci of softening were found in the cerebral cortex. Nerve cells in the foci were shadowy or had disappeared. No glial reaction was noted.

Few signs and symptoms of a focal neurological nature have been reported under such circumstances. In nonfatal cases, anesthesia of a leg and loss of vision have been noted (MACCLATCHIE 1931), as has also transitory paraplegia with anesthesia of the lower limbs (BEHNKE 1932; BROWN 1931).

The *cause* of serious reactions following ascent from a depth which excludes N_2 bubble embolism as a factor has long been the subject of inquiry. EWALD and KOBERT (1883) noted that arterial air embolism could be induced in dogs and other animals by raising the pressure of the air in the lungs. The degree of pressure required was between 50 and 90 mm. Hg. Air embolism and pulmonary

interstitial emphysema (without hemorrhages) occurred when air was slowly introduced into the lungs under a relatively low pressure, and air embolism and pulmonary hemorrhage when the insufflation of the air was rapid and under relatively high pressure. From these observations, EWALD and KOBERT concluded that since air embolism could occur independently of emphysema and pulmonary hemorrhage, it must be due to the passage of alveolar air, under the influence of increased pressure, through "stomata" of the alveolar wall into the alveolar capillaries by a process of diffusion. This view has continued to be held by RÖSSLE (1947) and FELIX and LOESCHCKE (1950b), who also believed that the hemorrhages in the lung were purely coincidental to the air embolism.

In repeating the experiment, POLAK and ADAMS (1932) tied a cannula filled with normal saline solution into the carotid of dogs so as to act as a trap for any air bubbles which might be circulating in that artery, and then raised the intrapulmonary pressure to 60 mm. Hg for 10 seconds; the peripheral venous pressure (internal jugular) rose, the venous flow from the lungs receded, but no bubbles appeared in the carotid trap. When, however, they raised the intrapulmonary pressure to 80 mm. Hg for 10 minutes the same effects on the arterial and venous pressures were noted, and, in addition, numerous air bubbles appeared in the carotid trap a few minutes *after* the intrapulmonary pressure had been released. When the intrapulmonic pressure was raised to 100 mm. Hg the animal's respiratory movements ceased, but the heart continued to beat for approximately 2 minutes.

Post-mortem studies of animals exposed to the 80 mm. Hg increase revealed extensive interstitial emphysema around the intrapulmonary veins, in the region of the hilus of the lungs, and in the mediastinum. Moreover, there was alveolar rupture and hemorrhage mainly in regions adjacent to perivenous emphysematous tissue. Air was found in both sides of the heart (as much as 77 cc.) and in coronary, visceral and meningeal vessels. No bubbles were found in the pulmonary lymphatics or thoracic duct.

The postulated sequence of events was: 1. rupture of alveolar walls and vessels as the result of the increased intrapulmonary pressure, 2. the forcing or aspiration of air into the ruptured vessels, and 3. *after* the release of intrapulmonary pressure, the passage of the bubbles to the left heart and into the general circulation.

The key to the conclusion that the air embolism was due to rupture of alveolar walls and their vessels rather than to diffusion of air through "stomata" of the lung lay in the results of further experiments, namely that air embolism failed to occur following an increase of intrapulmonic pressure to 80 mm. Hg when expansion of the lungs was restricted by bandaging the chest. The conditions are analogous to those encountered when an individual compresses his lung, through expiratory efforts, with the glottis closed, thus raising his intrapulmonary pressure as high as 100 mm. Hg: during expiration the lung volume remains unaltered because the chest does not expand. In considering this point, MACKLIN and MACKLIN (1944) commented:

"There is room here for generalization: Contracted bases are stronger; enlarged bases are weaker. The strength of the base is in inverse relation to its area. Stretching thins and weakens the base. Although air embolism may not occur under pressures as high as 100 mm. Hg, pulmonary interstitial emphysema may and does happen, as shown by its sequels, pneumomediastinum, subcutaneous emphysema and pneumothorax in women in labor, children with obstructive laryngitis, etc., where pressures are probably much less than 100 mm. Hg in excess of normal . . . pressure in the alveoli may have to be much higher to cause air embolism than it does to cause pulmonary interstitial emphysema."

Of the causation of pulmonary interstitial emphysema, they stated, in essence, that the basic cause . . . is the establishment of a *pressure gradient* from alveolus to vascular sheath. When the alveoli lack support owing to reduction of vessel caliber brought about by the increase in intrapulmonary pressure, they rupture. The alveoli can withstand high pressures inside them, if the pressure outside is equally high; they can be made to rupture at atmospheric pressure if the surrounding (supporting) pressures are too low.

Returning to the subject of *venous and arterial pressure changes* referred to in connection with pulmonary insufflation with air, the interpretation given by HALDANE and PRIESTLEY (1935) (see also DRIPPS [1952]) is that the rise in peripheral venous pressure is due to blockage of the veins entering the right heart by the forcibly expanded lungs, and the fall in systemic arterial pressure to the consequent diminution in left ventricular filling. The volume of blood necessary for effective circulation is thus significantly reduced. That the pulmonary arterial pressure actually falls under such conditions has been demonstrated by BJURSTEDT and HESSER (1953).

In anesthetized dogs in which simultaneous recordings were made of the intratracheal, intrathoracic and intra-abdominal pressures and the mean pressure of the femoral artery, BJURSTEDT (1953) found that upon positive pressure inflation of the lungs the intra-abdominal pressure increased considerably less than the intrathoracic. Thus he reasoned that in pulmonary overdistention during rapid decompression the pressure gradient developing between thorax and abdomen causes a pooling of blood not only in the peripheral venous system but also in the abdominal vessels and, as a consequence, a defective filling of the right heart. Although in the classical Valsalva experiment in normal human beings there is no difference in the increase in intrathoracic and intra-abdominal pressures, in the "passive" Valsalva experiment—an entirely artificial situation—the changes in pressure are of the same order as in the dog experiments. This has been shown by BJURSTEDT, WOOD and ASTRÖM (1953), who drew the conclusion that the results of the "passive" Valsalva experiment are applicable 1. to ascent under water if the airways are not kept open and 2. to positive pressure breathing used in aviation. The applicability is even more apparent if the subject is exhausted or unconscious, since under these conditions abdominal muscular tone is impaired and the abdominal venous pooling exaggerated.

B. Explosive decompression to altitude.

"Explosive decompression" refers to decompression to altitude in less than 1 second, and "rapid decompression" to decompression in more than 1 second. These terms are used for the sake of convenience, for actually no factor has yet been found which justifies a distinction between explosive and rapid decompression.

In explosive decompression the degree that can be withstood safely is determined by the rate and the relative expansion of the body gases (LOVELACE and GAGGE 1946; SWEENEY 1944; SWEENEY and JOFFE 1945). No adverse effects occur when an individual, breathing pure O_2, is explosively decompressed from 20,000 to 40,000 ft. (6,100 to 12,200 m.) and returns to 38,000 ft. (11,580 m.) and stays there for 90 minutes (HITCHCOCK 1951). He will, however, be as subject to decompression sickness of N_2 origin as an individual decompressed at conventional rates. If, however, the explosion is more severe the bends incidence will be appreciably higher (HITCHCOCK 1951). Decompression to altitudes of 38,000 to 62,300 ft. (11,580 to 19,000 m.) has been found to be safe provided the individual is recompressed within a few seconds (BENZINGER 1950; LUFT 1950; SMITH 1942). Under nonpressurized conditions, a longer sojourn leads to death from anoxia within a few minutes even through pure O_2 is breathed. At 52,000 ft. (15,850 m.), for example, unconsciousness from anoxia occurs in approximately 12 seconds and death soon afterwards (ARMSTRONG 1952). Serious hypoxia can, however, be prevented for at least 5 minutes at altitudes of 40,000 to 50,000 ft. (12,200 to 15,250 m.) through the use of pressure-demand oxygen equipment (LUFT et al. 1953). The altitude of 52,500 ft. (16,000 m.) is critical for the maintenance of life under nonpressurized conditions, for at that altitude the partial pressures of alveolar H_2O vapor (47 mm. Hg) and CO_2 (30 mm. Hg)

are equal to the total atmospheric pressure (77 mm. Hg), and hence at this altitude and above, the lungs are incapable of oxygenating blood even in an atmosphere of pure O_2 (GELFAN et al. 1947; LIVINGSTON 1951).

On explosive decompression, *expansion of the gas in the gastrointestinal tract and lungs* occurs, and as a consequence the intra-abdominal and intrathoracic pressures increase. The increased intra-abdominal pressure persists until the original barometric pressure returns to normal or until the gas escapes from the gastrointestinal tract. On the other hand, the increase in intrathoracic pressure is extremely evanescent, for air can easily be expelled from the lungs. If, however, the ambient atmospheric pressure falls at a rate greater than the lungs can decompress through the upper air passages, the intrapulmonic pressure increases, and, when excessive, may rupture alveolar walls, causing hemorrhages which usually do not manifest themselves clinically (BERG et al. 1943; BURCKHARDT et al. 1951; SMITH 1942). The pulmonary hemorrhages of dogs similarly decompressed were considered by EDELMANN et al. (1946) to be due mainly to the thrust of the periphery of the lungs against the thoracic cage as a consequence of the suddenly increased intrapulmonary pressure. The same conclusion was reached by RÖSSLE (1947).

Heart rate and blood pressure are also affected in explosive decompression. HITCHCOCK (1951) has observed that significant transitory falls in blood pressure occur following pressure changes of more than 1124 mm. Hg per second, the extent of the fall varying inversely with the rate of decompression and directly with the range of decompression. Bradycardia also developed. Bilateral vagotomy prevented the bradycardia, but it merely reduced the blood pressure drop. The fall in blood pressure was, however, prevented by denervation of the pulmonary arteries, indicating that the fall was mediated by hemodynamic reflexes (WHITEHORN 1948; WHITEHORN et al. 1946).

HITCHCOCK (1951) has shown that rats subjected to multiple explosive decompressions in the non-fatal range failed to exhibit alterations in *maze tests*, and dogs similarly decompressed revealed no deterioration in *conditioning*. In a study of 19 dogs exploded from a simulated 10,000 to 50,000 ft. (3,050 to 15,250 m.) and rapidly recompressed to normal barometric pressure within 1 or 2 minutes and then sacrificed, he found hemorrhagic lesions in the lungs in 13 and in or adjacent to the mitral valve in 3; and in 15 of the brains there were subdural ecchymotic hemorrhages encompassing the sagittal sinus in 4, petechial hemorrhages in the walls of the lateral ventricles of the brain in 1, and in both locations in 1.

Pathological changes occurring in dogs explosively decompressed from 10,000 to 72,000 ft. (3,050 to 21,900 m.) in 0.035 second have been reported by COLE et al. (1953). In *series I* the animals were held at the terminal pressure for 2.5 minutes and then recompressed to ground level in 1 minute; in *series II* the animals were recompressed immediately after decompression (1 min.), and in *series III* the animals were also recompressed immediately but approximately at the rate of a free fall (about 7 min.), and thus served as controls to eliminate any possible effects of rapid compression. All animals were sacrificed within 10 minutes if death did not occur before that time. In general, the same lesions were found in all animals, but were most severe in series I. Pulmonary atelectasis, hemorrhage and emphysema were noted in all. The atelectasis was ascribed to a positive intrapleural pressure resulting from the development of vapothorax immediately after the decompression. Refilling of the lungs after recompression was prevented in some areas trough the occlusion of bronchi and bronchioles by hemorrhages. Myocardial damage in the form of muscle fiber fragmentation

and hemorrhage was assumed to be the cause of death. No air emboli were noted. In all 3 series of experiments, hemorrhages up to 2 cm. in diameter were widespread. Subarachnoid hemorrhages are illustrated in Fig. 27.

Especial attention was paid by BURCH et al. (1952) to the *cardiac alterations* occurring in dogs similarly decompressed, i.e., to 74,000 ft. (21,000 m.; 30 mm. Hg) in 0.02 second, and recompressed to ground level after a minute or longer. There was EKG evidence of serious damage of the myocardium, which was mainly due, they concluded, to the stretching of the myocardium by the expansion of gas within the heart.

FEGLER and BANISTER (1946) have found in rabbits, and LIVINGSTON et al. (1947) in rats, explosively decompressed to a simulated altitude of 50,000 ft.

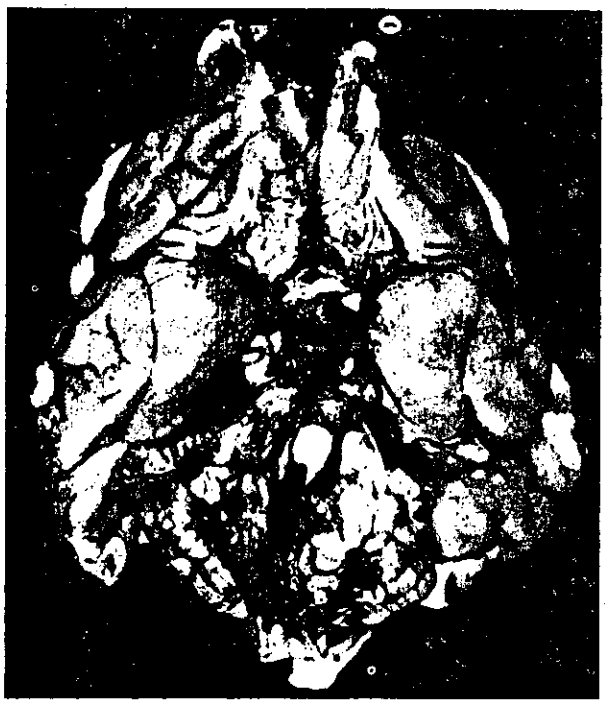

Fig. 27. Brain of dog explosively decompressed from a simulated 10,000 to 72,000 ft. (3,050 to 21,950 m.) in 0.035 second and immediately recompressed to ground level in 1 minute. There is subarachnoid hemorrhage in the region of the pons, medulla oblongata, and optic chiasm. (Dog 52-1; Ohio State Univ. Photo No. A-33032-2; courtesy of Dr. C. R. COLE and Dr. F. A. HITCHCOCK, Columbus, Ohio.)

(15,250 m.) and higher that the lungs were completely consolidated and liverlike and sank when they were placed in water. The blood flow through the capillary bed had been virtually occluded. The observation that the lungs of some animals contained hemorrhages and others not was considered to be related to the phase of respiration at the moment of the decompression.

If at the moment of explosive decompression an individual voluntarily or inadvertently holds his breath at maximal inhalation with the glottis closed, or under experimental conditions the trachea is occluded, an increase of intrapulmonary pressure to 80 mm. Hg or more over the ambient hydrostatic pressure will give rise to *mediastinal emphysema and/or air embolism* (BENZINGER 1943; BERG et al. 1943; DÖRING and KÖNIG [cited by BENZINGER 1950]; GREELEY et al. 1943; HEBB 1941; TROWELL 1941a). In the normal human male an intrapulmonic pressure of 20 to 25 mm. Hg is necessary to distend the chest to the

full inspiratory capacity (relaxation pressure). Shortly after dogs with trachea momentarily clamped shut had been explosively decompressed to 33,000 to 39,500 ft. (10,000 to 12,000 m.), DÖRING and KÖNIG found bubble-laden blood passing through a glass cannula which had been inserted into the carotid. In a post-mortem study of these animals, RÖSSLE (1947) (see also BENZINGER [1943]) observed bubbles in various regions, distention of the lungs, peribronchial bleb formation, pulmonary hemorrhages, rupture of pulmonary veins, pulmonary edema in some animals, and severe mediastinal and cervical emphysema.

Accounts of harmful effects of explosive decompression in human beings are rare. Two instances were described by BENZINGER (1950). In *one*, in which the individual was exploded from 9,800 to 32,800 ft. (3,000 to 10,000 m.), consciousness was lost 15 seconds later. During the descent, cyanosis and clonic contractions of left facial muscles were noted. When, 3 to 5 minutes after the incident, consciousness was regained, a severe speech disorder and ataxic gait were evident. Half an hour later he had completely recovered. In the *other*, at the moment of explosive decompression to 39,400 ft. (12,000 m.) the individual felt an intense pain in his chest. During the descent, which lasted 25 seconds, his right arm became numb and motionless. Consciousness was not affected. A sore feeling persisted in his chest for 2 days, after which he was well again. Healed pulmonary tuberculosis flared up in this individual as a result, apparently, of the explosion, and not until many months afterwards was it brought under control.

Summary and comment.

The primary decompression phenomena in divers and in individuals explosively decompressed to altitude are very similar. Air embolism is the chief hazard under both conditions: in the diver, using an artificial lung, when he holds his breath during ascent, and in the individual being explosively decompressed when at the moment of the explosion he holds his breath at maximal inhalation with the glottis closed. For air embolism to occur it is necessary that the intrapulmonary pressure rise approximately 80 mm. Hg higher than the ambient pressure. Rupture of the alveolar capillaries, upon which the introduction of air into the circulation depends, is the result of the establihsment of a high pressure gradient between the alveolar wall and the sheath of alveolar vessels. Pulmonary interstitial emphysema may occur as a consequence of a lesser increase in the pressure gradient.

The incidence of decompression sickness (due to N_2 bubble formation) in explosive decompression varies with the rate and range of the decompression. The incidence is no different from that in decompression at conventional rates when the rate-range of the explosion is moderate, but is it significantly higher when the rate-range is high. Pearl divers, sponge fishermen and the like are subject to both decompression sickness and air embolism.

Little information is available on CNS lesions resulting from air embolism in divers, for the reason that death occurs too rapidly for the lesions to become established. In one exceptional case, in which the patient survived for 42 hours, the cerebral lesions were identical with those of air embolism (p. 1658). Studies of the CNS of animals explosively decompressed and sacrificed shortly thereafter have thus far disclosed little more than leptomeningeal hemorrhages.

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A review of blood changes associated with compression-decompression: relationship to decompression sickness

R. B. PHILP

Department of Pharmacology, The University of Western Ontario, London, Canada N6A 3K7

Philp, R. B. 1974. A review of blood changes associated with compression-decompression: relationship to decompression sickness. Undersea Biomed. Res. 1(2): 117-150.—Blood cellular and chemical changes associated with compression-decompression of experimental animals and human subjects are reviewed. Existing evidence suggests that diving entails multiple physiological stress factors which probably account for many of the observed changes including elevated levels of isoenzymes, catecholamines, and cortisol as well as leucocytosis and possibly reductions in red-cell count. Decompression of both experimental animals and human subjects is commonly associated with a reduction in circulating platelet count which may persist for 2-3 days postdive. Animal data suggest that this may be due to the adherence of platelets to *silent* bubbles. Some antiplatelet drugs have been shown to reduce the morbidity and mortality of decompression sickness in animals and to retard the postdive loss of platelets in man. Hemoconcentration is a not uncommon finding in clinical bends and limited evidence of associated platelet loss has been obtained. The practical and theoretical potential of pharmacological agents in the treatment of decompression sickness is reviewed. (210 references).

decompression sickness
blood chemistry
platelets and red cells
isoenzymes
pharmacological treatment of bends

"Blood will tell but often it tells too much"

Donald R.P. Marquis

Decompression sickness (DS), variously referred to throughout its history as the bends, caisson disease (in reference to tunnel workers or *sand hogs*), compressed air illness, and dysbarism, is a syndrome which results when people are subjected to an overly abrupt and extensive reduction in environmental barometric pressure. As the various names imply, it has been encountered not only by deep-sea divers but by high-altitude aviators and men employed in underground engineering projects in which compressed air is used to hold back ground water. It also constitutes a potential hazard for astronauts and even for commercial air passengers should an accidental rapid loss of cabin pressure occur. The condition appears to be the result of the formation of bubbles of inert gas (chiefly nitrogen when air is the breathing gas) in fluids and tissues of the body. Inert gases like nitrogen are dissolved in

body tissues and fluids and, with sufficient time, reach a state of concentration equilibrium with the environment. If the reduction in barometric pressure exceeds the rate at which the dissolved nitrogen can diffuse across the various membrane barriers of the body and be eliminated in the expired air, a state of supersaturation occurs and bubbles may form. The situation is analagous to the precipitation of solute from a supersaturated solution and it has frequently been compared to the formation of bubbles which accompanies the removal of the cap from a bottle of carbonated beverage.

The symptoms and signs of DS are protean, ranging in severity from skin rash and joint pain to central nervous system disturbances, respiratory difficulties, paralysis, and acute circulatory shock, depending presumably upon the extent and location of the offending bubbles. Treatment classically has revolved around the principle of recompression of the victim with a view to driving the bubbles back into solution, with moderate, controlled decompression to allow the harmless diffusion and elimination of inert gas. Breathing oxygen toward the end of the therapeutic decompression has greatly expedited treatment, the aim being to produce a more favorable concentration gradient for the elimination of nitrogen across the alveoli of the lungs.

The central position of the gas bubble in the etiology of decompression sickness is by now so widely accepted that it hardly seems necessary to document the supporting evidence here. It has been pointed out (Buckles 1968) that "All the predictive models that are used to compute 'safe' decompression schedules involve some considerations about the formation and growth of bubbles *in vivo*." Behnke (1971) emphasized the importance of the particular location of bubbles even further, stating "Intravascular bubbles form the crux of our discussion and the prime tissue involved is circulating blood."

Agreement as to the principle causative agent of the condition has not always been so universal. The monumental work of Paul Bert (1878) established the central role of the bubble in DS yet disagreements on this point persisted for years. Pioneers in the field of pressure physiology and medicine, hampered as they were by incomplete knowledge both of physics and physiology, often formulated novel and bizarre theories to explain the syndrome of caisson disease (Fryer 1968). One of these was the *congestion* theory which held that blood was forced under pressure from soft, compressible tissues into those protected by rigid structures such as the brain and spinal cord and that the signs and symptoms of the disease resulted either from hemorrhage occurring during the congestive phase or from anemia resulting from the sudden return of the blood to the periphery during decompression (Van Rensselaer 1891a). The frequency of spinal cord lesions in early victims of caisson disease, together with the oft-noted occurrence of clots and thrombi in soft tissues and organs examined post mortem, lent support to this theory (Van Rensselaer 1891b). Deaths in these instances, however, usually occurred days or weeks after the decompression and undoubtedly were secondary to paraplegia resulting from spinal cord injury during decompression. Andrew H. Smith (1894), consulting physician to the New York Bridge Co. during the construction of the Brooklyn Bridge, believed that activation of the clotting process was involved in the pathology of bends. He wrote "But meanwhile, the slowing of the current, or perhaps actual stasis, has brought about more or less serious and permanent results. Thrombi may have formed, affording material perhaps for emboli at more distant points."

Despite Smith's erroneous views on the cause of decompression sickness (he was an exponent of the congestion theory) his words were nonetheless prophetic. On the basis of observations of the fine vasculature of decompressed rats, Swindle (1937) and End (1938) proposed that the sludging of red cells led to the formation of emboli and petechial infarcts

and that these were the primary causative agent in decompression sickness with bubbles being a complicating factor. The hypothesis failed to impress contemporary workers in the field. Coming as it did at a time when new knowledge was accumulating on nitrogen desaturation of the human body (Behnke 1937, 1945; Behnke and Willmon 1941; Willmon and Behnke 1941), and when more effective decompression tables were being developed as well as better treatment procedures including oxygen breathing to assist nitrogen elimination (Behnke and Shaw 1937; Yarbrough and Behnke 1939) such a theory, which relegated the bubble to a secondary role, was bound to encounter skepticism. Research on the effects of decompression on blood languished for a quarter of a century, except for sporadic observations, whilst the advancement of the art and science of diving, and the application of the laws of physics thereto, continued apace.

Despite these advances, a nagging suspicion persisted that other causative factors might be involved in the pathogenesis of DS because certain observations were difficult to reconcile with the hypothesis that the bubble was the sole etiological agent. Among these were the sometimes prolonged lapse of time between the end of decompression and the onset of symptoms, the occasional failure of recompression to relieve the victim, wide variations in susceptibility (even within an individual subjected to the same decompression profile on different occasions), and the great difficulty in demonstrating the presence of bubbles in affected individuals. These considerations were reviewed by Holland (1969).

Regarding the demonstration of bubbles in victims of DS, the advent of the Doppler ultrasonic probe appears to have yielded convincing evidence that intravascular bubbles are indeed associated with decompression, even in the absence of overt signs of the bends (Smith and Spencer 1970; Rubissow and McKay 1971; Spencer and Oyama 1971; Powell 1972; Spencer and Clarke 1972; Shilling and Werts 1972). Thus the central position of the bubble has been reaffirmed. However, in the reaffirmation a further paradox has been revealed—the presence of the etiological agent has been detected frequently in the absence of the disease. Were the bubble to be viewed as a microorganism this would be a clear violation of one of Koch's postulates; namely, in order to be identified as the causative agent of a disease the microorganism must elicit the appropriate symptomatology when it is introduced into a susceptible animal. The significance of secondary biological influences upon susceptibility to decompression sickness becomes readily apparent.

A resurgence of interest in the role of the blood in decompression sickness followed observations of French investigators that compression with air caused a transient reduction in the whole-blood clotting time of rats and that the tranquilizer chlorpromazine prevented this hypercoagulability and afforded some protection against decompression sickness in rats and rabbits (Sautet, Jullien, Leandri, and Rampal 1961). French workers (Laborit, Barthélémy, and Perimond-Trouchet 1961) also claimed that the anticoagulant heparin improved the survival rate of rabbits rapidly decompressed from high pressure. Barthélémy (1963) advocated the use of heparin in the treatment of decompression sickness and described five cases of bends in divers in which heparin appeared to have elicited clinical improvement whereas recompression therapy alone had not. It is from this point in history that your reviewer takes up his task in earnest.

ALTERATIONS IN BLOOD COAGULATION

It would appear that compression-decompression may be associated with the development of a *hypercoagulable state*, evidence of which may be detected in the absence of overt signs of DS, providing the screening procedures are adequate. Such shifts toward increased

activity of the hemostatic mechanism do not usually exceed normal physiological limits in man but they may represent a prodromal state. Early animal experiments suggested that the hyperbaric environment itself might set the stage for hyperactivity of the clotting system which is subsequently triggered by a too-rapid decompression. Experiments with air-injected rabbits, however, indicated that the presence of an air-blood interface alone will activate the hemostatic mechanism. To date, little evidence is available concerning the state of the hemostatic process in individuals suffering from Type I or Type II bends. It may be that the changes are too subtle to detect unless normal, predive baseline values are available.

In 1933 Aggazzoti studied the clotting times in dogs and rabbits before and during decompression from 6-11 ATA. He found accelerated clotting in 12 of the animals but in 4 that seemed to show signs of decompression sickness the clotting time was prolonged. Much later, Jullien, Leandri, and Crozat (1958) found evidence of accelerated clotting using the heparin test and thromboelastography in experimental animals and human subjects decompressed too rapidly from a hyperbaric environment. The changes occurred at the end of decompression and they were not associated with detectable signs or symptoms of DS. Barthélémy (1963) reported a shortening of the clotting time during a sojourn at high pressure, which recovered to normal values provided decompression was relatively slow. The abnormality persisted, however, if the maximum permissible ascent rate was used and also appeared to be aggravated by elevated P_{O_2} or P_{CO_2} levels. Mazza and Pallotta (1963), using rabbits decompressed rapidly (15-20 sec) from 5 or 6 ATA, found evidence of hypercoagulability which was reversible in those which survived. Subsequently, they reported (Mazza and Pallotta 1964) that 8 days of premedication with chlorpromazine reduced clotting activity in rabbits and tended to prevent the hypercoagulability following decompression. Survival, however, was not significantly altered.

Using various animal models of decompression sickness, several investigators have demonstrated evidence of increased clotting activity including decreases in clotting factors (Ehm, Piechotta, and Schimpf 1971) and histopathological evidence of disseminated intravascular coagulation (Philp, Schacham, and Gowdey 1971; Albano, Burrano, Mazzone, LaMonaca, and Scaglione 1971). Wells, Bond, Guest, and Barnhardt (1971) observed increases in partial thromboplastin times in dogs decompressed in 10 min after 1 hr of breathing 95% N_2 and 5% O_2 at a pressure equivalent to 200 fsw (7.3 ATA). Inwood and Philp (1973) used a rat decompression model which yields a spectrum of severity of signs of decompression sickness and found a strong association between the severity of DS and the degree of disturbance in the hemostatic mechanism. Levels of Factors 5 and 8 were significantly elevated in moderately affected animals but greatly depleted in severely affected ones and in those which died (Fig. 1) even as compared to control rats which were killed with an overdose of sodium pentobarbital. Partial thromboplastin time (PTT) (Fig. 2) was significantly shortened in mild to severely affected rats but greatly prolonged in those which died and the Hicks-Pitney thromboplastin generation time and the thrombin time (TT) were prolonged in animals which died from DS (Fig. 3). There was evidence of significant levels of fibrin-fibrinogen degradation products (Fig. 4) in moderately and severely affected animals and in those which died from DS, the levels correlating with the severity of the attack. Similar findings were obtained in our laboratory using anesthetized rabbits injected intermittently with air via the carotid artery, thus suggesting that air-blood contact per se is sufficient to activate the clotting system, independent of the presence of compression-decompression. Earlier workers had noted the formation of fibrin deposits in the hearts of experimental animals with air embolism (Richardson, Coles, and Hall 1937); (Auer and Krueger 1946).

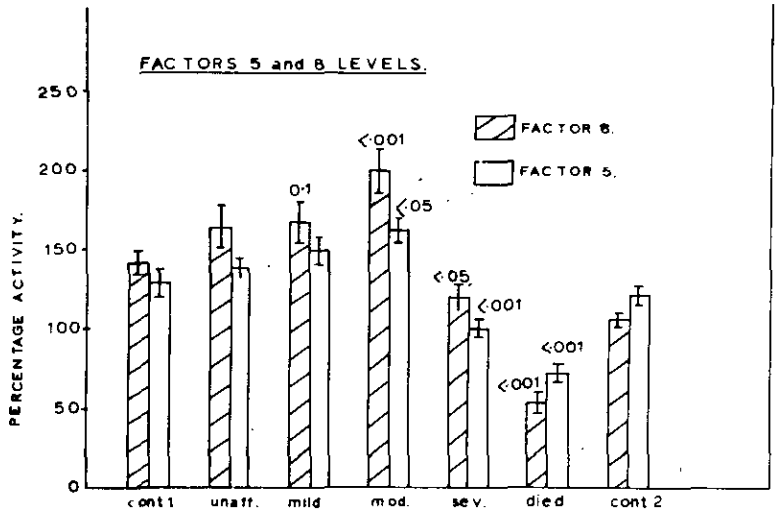

Fig. 1. Levels of Factors 5 and 8 of rats with varying degrees of severity of DS induced by 2 hr at 5.4 ATA, stage decompression in 15 min and treadmill exercise at simulated altitude (10,000 ft). Control group 1 received treadmill exercise at 1 ATA (no compression-decompression). To control the effects of morbid change, rats in control group 2 were similarly exercised after being given a lethal dose of pentobarbital IP. The lines at the top of the bars reflect the SEM of the measurements. The numbers above the bars are the p-values (from Inwood and Philp 1973).

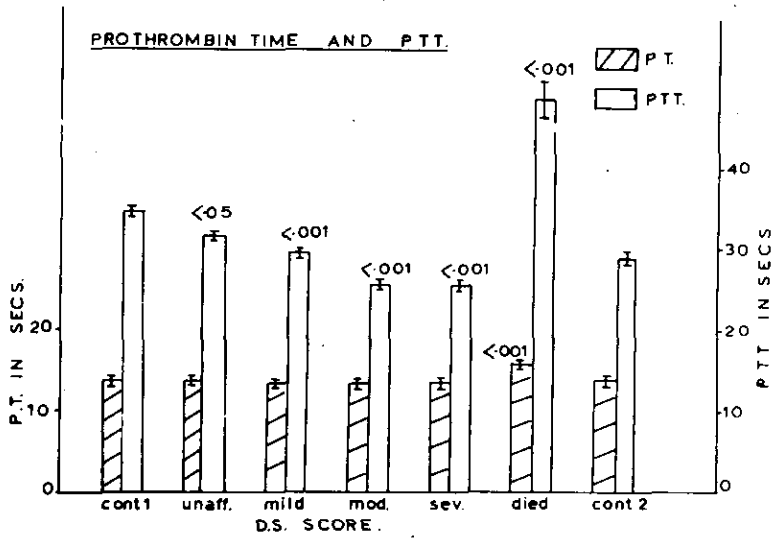

Fig. 2. Prothrombin and partial thromboplastin times, experimental conditions as described for Fig. 1. The lines at the top of the bars reflect the SEM of the measurements. The numbers above the bars are the p-values (from Inwood and Philp 1973).

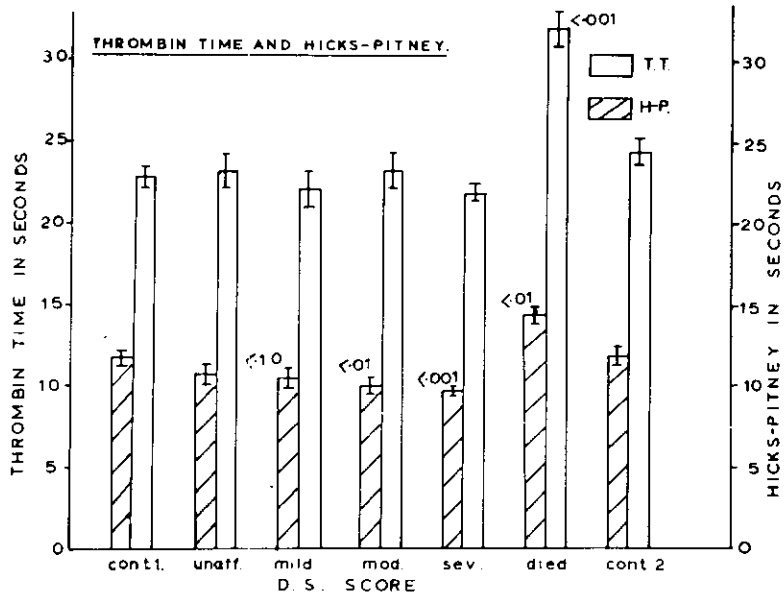

Fig. 3. Thrombin clotting times and Hicks-Pitney thromboplastin generation tests, experimental conditions described in Fig. 1. The lines at the top of the bars reflect the SEM of the measurements. The numbers above the bars are the p-values (from Inwood and Philp 1973).

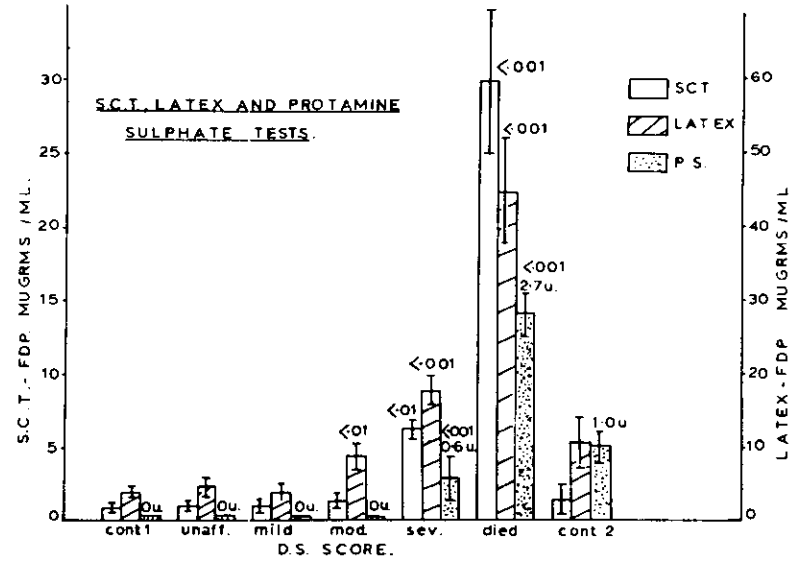

Fig. 4. Evidence of fibrinolytic activity as determined by the staphylococcus clumping test (SCT) and the latex agglutination method and evidence of fibrinogen-fibrin monomer complexes as determined by the protamine-sulfate test (PS). Experimental conditions as in Fig. 1. The lines at the top of the bars reflect the SEM of the measurements. The numbers above the bars are the p-values (from Inwood and Philp 1973).

In recent years, evidence of altered clotting activity after decompression has been observed in human subjects. In 1970 Sicardi reported an increased antithrombin rate of the order of 34% in three divers following decompression from a pressure equivalent to 200 msw (21 ATA) and pointed out that such increases were frequently associated with a hypercoagulable state. Livingstone, Achimastos, and Ackles (1971) using thromboelastography, demonstrated a shortening of the r time and k time after exposure and decompression of human subjects to 7 or 10 ATA, thus again suggesting a hypercoagulable situation. Our group (Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski 1972) performed an extensive examination of the hemostatic system in 16 human subjects decompressed on a continuous profile after 10 min at 10.4 ATA on air. There were 4 cases of Type I bends and 12 (including these 4) of *skin bends* (pruritis). When results from samples collected immediately after the end of decompression were compared with predive results, these affected divers showed a significant decrease in prothrombin consumption time, a significant decrease in Antithrombin III activity, and significant decreases in euglobulin lysis time and plasminogen activity (indicative of increased fibrinolytic activity). There was also evidence of increased circulating fibrin-fibrinogen split products. Although the absolute values for these tests remained within normal physiological limits, the changes were indicative of a shift to a more hypercoagulable state. Subsequently we reported (Philp, Inwood, Ackles, Radomski 1974) evidence of altered hemostasis, persisting for 24 hr or more postdive, including prolongation of thrombin generation times up to 24 hr postdive and a reduction in Antithrombin III activity up to 48 hr postdive. Bonin, Straub, Schibli, and Bühlmann (1973) found evidence of fibrinolytic activity and prolongation of the prothrombin time (PT) in divers decompressed after 2 hr at 10 ATA breathing a He-O_2 mixture. The changes in PT were more pronounced in individuals with Type I bends.

CELLULAR CHANGES

PLATELETS

The evidence from animal experiments strongly suggests a role for the involvement of platelets in DS. Adherence and aggregation of platelets to the bubble surface has been demonstrated and platelet microthrombi have been shown to be present in severe cases of DS in experimental animals. A thrombocytopenic response to compression-decompression in man has been observed in conjunction with several dive profiles, largely in the absence of any overt signs of DS. Preliminary evidence indicates that the extent of platelet loss in man may be influenced by the state of the platelet population in an individual, so that subjects with an inherent platelet defect may be less likely to lose platelets while those with highly active platelets (as determined by in vitro tests of platelet function) may lose more than normal subjects. The question of whether the loss of platelets is a compresion phenomenon or is due to decompression per se appears to have been answered. The continuing loss of platelets for 24-48 hr may be due to damage incurred during decompression by a cohort of the platelet population, such that their normal life expectancy is shortened.

Information concerning the disposition of platelets in clinical cases of Type I and Type II DS is virtually nonexistent. In the face of experimental evidence gleaned both from animals and from human subjects, one would be inclined to believe that any sign of DS, however mild, if accompanied by evidence of thrombocytopenia, ought to be viewed as a potentially serious situation.

Although Geller (1941) postulated that platelets could interact with bubbles he provided no supporting evidence. Jacobs and Stewart (1942) may have been the first to observe an effect of bubbles on platelets. Severing the tips of the tails of decompressed rats, they saw bloody froth issue from the vessels and, upon microscopic examination, found that the bubbles were surrounded by platelet aggregates. They speculated that such aggregates might occlude fine blood-vessels. Our laboratory used a standardized animal model for decompression sickness which consisted of a 2-hr exposure to 5.3 ATA followed by stage decompression over 17 min and exercise at a simulated altitude of 10,000 ft (696 millibars or 0.69 ATA). There was a loss of circulating platelets following this procedure, the extent of which correlated with the observed severity of DS (Philp, Gowdy, and Prasad 1967; Inwood and Philp 1973). Other experiments (Philp and Gowdey 1969; Clark, Philp, and Gowdy 1969a) demonstrated that rats rendered thrombocytopenic by an immunological procedure were not protected against DS, and those which were thrombocytotic during the rebound recovery phase had a significantly higher incidence of DS than control rats. Moreover, rabbits which were slowly infused with air intravenously showed a progressive fall in the circulating platelet count. Others (Ehm et al. 1971) subsequently confirmed this observation in decompressed rabbits. Somewhat earlier Kahn, Suetsugu, Alkalay, Platthy, and Stein (1966) found that the increased resistance to blood flow through the lungs, which followed the injection of a large air embolus, was largely absent in dogs rendered thrombocytopenic. They speculated that pulmonary vasoconstriction was due to serotonin released from platelets.

Histopathological evidence of platelet involvement in experimental DS has also been accumulating. In 1963 Clay reported on a series of dogs decompressed in 10 min after 1 hr at a pressure of 6 ATA and found 14 of 31 dogs had platelet microthrombi in blood vessels of the lungs. Adebahr and coworkers (Adebahr and Kupffer 1967; Adebahr and Stack 1969; Adebahr 1971) saw platelets and platelet aggregates surrounding intravascular bubbles in rabbits killed by the intravenous injection of air.

Philp et al, (1971), using the rat decompression model described above, showed that there was a positive correlation between the extent of lung pathology (microthrombi) and the severity of DS and that the intravenous infusion of air into rabbits produced multiple microthrombi in lung vessels consisting of air bubbles, platelet aggregates, and sludged red cells. Direct, visual evidence of platelet-bubble interactions was provided by our laboratory (Philp, Inwood, and Warren 1972; Warren, Philp, and Inwood 1973). We were able to develop a method for the in situ fixation of tissues which permitted the examination of blood and bubbles by electron microscopy. Using explosively decompressed rats with massive intravascular bubble formation, we showed that bubbles acquired a coating, approximately 200 Å in thickness, which appeared to consist of fibrinogen primarily. Lipid micelles also became entrapped at the air-blood interface, and platelets appeared to be selectively attracted to the interface with platelet adhesion progressing to platelet aggregation (Fig. 5). A striking similarity between this reaction and blood-foreign surface reactions in general was noted. Stegall, Smith, and Hildebrandt (1972) reported a marked (> 50%) reduction in circulating platelet counts of minature swine 24-48 hr after decompression from a hyperbaric environment. This was preceded by a significant increase in platelet adhesiveness immediately postdive.

Sicardi (1970) was the first to note a loss of platelets in human subjects following decompression. He reported a 37% reduction in the circulating platelet count of three divers following decompression from a simulated depth of 200 msw (21 ATA). The following year Bennett and Gray (1971), reporting on a 1500 fsw (46.5 ATA) dive, found that two of the

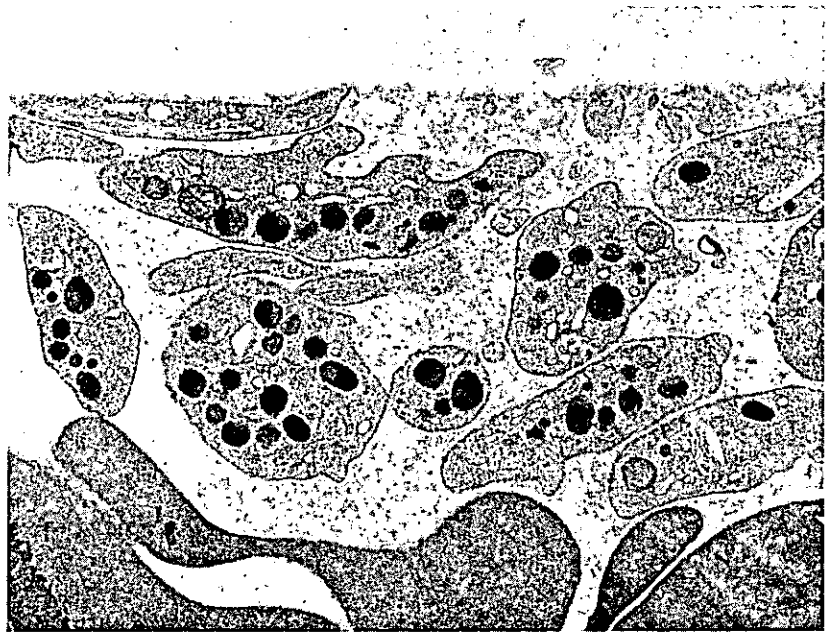

Fig. 5. Electron micrograph (x15,000) of platelets adhering to a blood bubble interface and to each other. The bubble is the clear area at the top of the photo. Deformed red cells can be seen at the bottom of the photo (courtesy Prof. B.A. Warren, Dept. Pathology, U.W.O.).

diving subjects lost 78,000 and 135,000 platelets/mm^3 of blood; the latter diver developed Type I bends near the completion of decompression. Not all investigators have confirmed a platelet loss following decompression. Bühlmann, Matthys, Overrath, Bennett, Elliott, and Gray (1970) found no significant change in platelet count immediately following a saturation exposure of divers to 31 ATA on a HeO_2 breathing mixture. Philp, Ackles, Inwood, and Livingstone (1972) found a mean decrease in circulating platelet count of 11.9% ± 3.35 (SEM) in 16 divers decompressed on a continuous, pneumatic analogue computer profile after 10 min at 10.4 ATA of air. There was, however, no correlation between the degree of platelet loss and the occurrence of Type I bends or skin bends. In addition, the adhesiveness of platelets to glass beads was significantly increased in 12 of the diving subjects who displayed decompression-associated signs and symptoms which included pruritis and skin rash and four cases of Type I bends. Such an increase was not observed in the four unaffected individuals. The megathrombocyte index (i.e. those platelets having a transverse diameter $>2.5\mu$ when examined microscopically in stained smears) was significantly increased in all divers but much more so in those affected with skin bends or Type I bends. These large platelets are believed to be young, newly released ones (Garg, Amorosi, and Karpatkin 1970).

Martin and Nichols (1972) recorded the unique observation that the circulating platelet count continued to fall for about 72 hr after a 1-hr exposure to a simulated depth of 100 fsw (4.1 ATA). These authors used a stage decompression procedure proven to be exceptionally free of any incidents of DS in nearly 200 open-sea dives. The platelet loss

averaged about 30% at the lowest point. Philp, Inwood, Ackles, and Radomski (1974) subsequently confirmed this observation in two separate experiments in which the British dive profile was reproduced and in an additional experiment in which the profile cited above (Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski 1972) was used. Again, postdive increases in platelet adhesiveness were observed which preceded the major fall in circulating platelet count. The megathrombocyte counts rose progressively after decompression, with a steep increase at a time (96 hr postdive) corresponding to the return of the platelet counts toward normal levels (Fig. 6). Platelet aggregation in response to

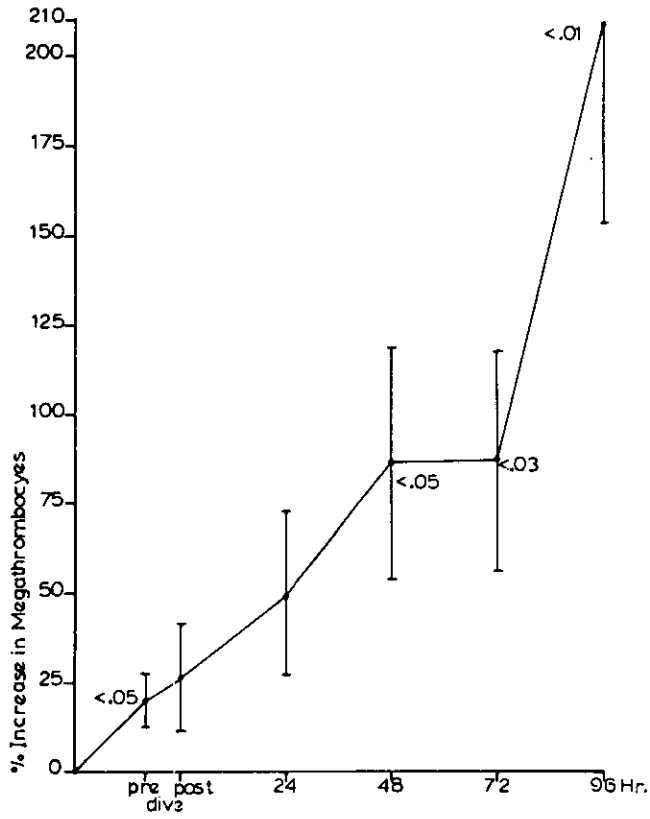

Fig. 6. Megathrombocyte indices before and after a simulated dive to 100 ft (air). The megathrombocyte index rose sharply at 96 hr postdive, a time corresponding to the return of platelet counts toward normal values. Megathrombocytes (platelets with a transverse diameter $> 2.5\mu$) are believed to represent newly released platelets. The lines at the top of the bars reflect the SEM of the measurements. The numbers above the bars are the p-values (from Philp, Inwood, Ackles, and Radomski 1974).

adenosine diphosphate (ADP) was also studied but no significant changes were noted in association with decompression. The progressive fall in circulating platelet count has also been seen under operational diving conditions. Philp, Freeman, Francey, and Ackles (1974)

performed platelet function and hematological studies on seven divers before and after a 6-7 day saturation exposure in an underwater habitat located in 50 ft of seawater off Freeport, Grand Bahama Island (Wicklund 1972). Two subjects were worthy of special note in that they both lost over 50% of their circulating platelet count 24 hr after surfacing. One of these divers had been engaged in a series of daily decompression dives to 150 fsw for several days prior to the experiment. He had not dived for the immediate 2 days preceding it. During this control period his platelet count showed an increase, thus indicating that it was probably recovering from the previous diving activities and that he had a high percentage of young platelets which are believed to be more biologically active (Zbinden, Grimm, and Muheim 1971; Karpatkin 1972). The other subject was shown to have spontaneous platelet aggregation, a phenomenon reported to be sometimes associated with idiopathic, peripheral thrombosis (Vreeken and Van Aken 1971; Friedlander, Cook, Hawkey, and Symons 1971; Biermé, Boneu, Guiraud, and Pris 1972). It is conceivable that these two individuals lost more platelets than most subjects because they both had a highly-reactive platelet population. Again, an increase in platelet adhesiveness preceded the loss of platelets as did an increase in platelet aggregating activity in response to ADP. Megathrombocyte indices increased markedly at a time when the platelet count was returning toward normal values. One other subject was mildly thrombocytopenic before the dive, possibly because of recent drug medication. His platelet count doubled while under pressure, suggesting that thrombopoiesis was not seriously compromised.

This laboratory has previously observed platelet abnormalities which appeared to influence the extent of platelet loss (Philp, Inwood, Ackles, and Radomski 1974). Two diving subjects were studied whose platelets lacked the release reaction in response to ADP or epinephrine. This anomoly appears to be present in about 10% of the population and is sometimes associated with a mild hemostatic defect such as easy bruising and it is similar in appearance to that caused by the ingestion of aspirin (Weiss, Chervenick, Zaluski, and Factor 1969). Neither of these subjects lost significant numbers of platelets after decompression, in contrast to their companions. Kindwall (1972) compared the platelet counts of two groups of tunnel workers, one of which had been operating at about 3.4 ATA for 1 week while the other had been working in free air. The mean platelet count of the compressed air workers was the same at any acceptable level of significance.

Recent experiments with the rat decompression model in our laboratory (Inwood and Philp 1973) showed that platelets collected from rats with moderate-to-severe DS were less senstive to ADP-induced aggregation than those of control rats (Fig. 7). We postulated that this was likely due to the consumption of the most active platelets in a peripheral, microthrombotic process so that the remaining platelets consisted of a less reactive, possibly senescent, cohort. A significant reduction in the circulating platelet count was also seen in these rats (Fig. 8). French workers (Broussolle, Stoltz, Mainart, Hyacinthe, and Pietrini 1973) likewise studied platelet aggregation in rats following a decompression accident and reported similar findings, reaching the same conclusion as we did.

RED CELLS

Very few observations have been made on the effects of decompression on red-cell function. Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski (1972) noted a significant increase in the number of reticulocytes seen in a group of subjects with skin bends or Type I bends occurring after decompression. This was not observed in

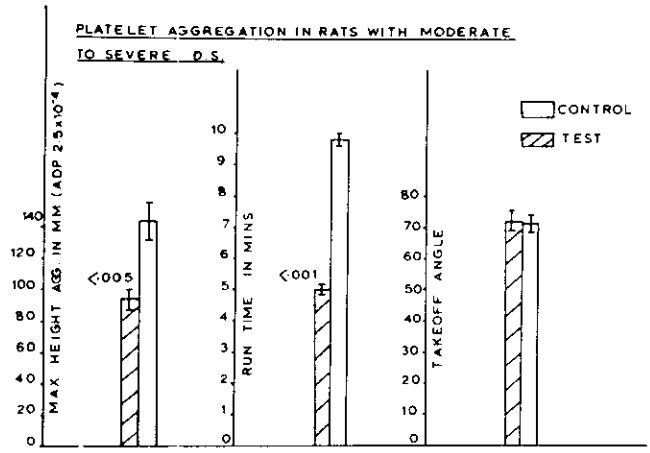

Fig. 7. Platelet aggregation in response to adenosine diphosphate in rats with moderate to severe DS as compared to control rats. A significant decrease in aggregating activity, as evidenced by a decrease in curve height and an increase in the time to onset of aggregation (run time) was observed in the rats with DS. This was felt to be due to the disappearance of the more active platelets from the circulation (see Fig. 8). The lines at the top of the bars reflect the SEM of the measurements. The numbers above the bars are the p-values (from Inwood and Philp 1973).

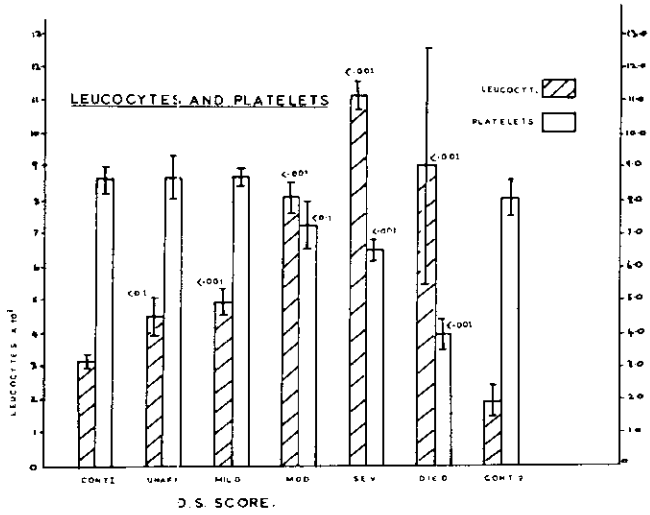

Fig. 8. Changes in platelet and leucocyte counts of rats with varying degrees of severity of DS. Platelet counts tended to decrease with severity whereas leucocytes increased (experimental conditions as in Fig. 1). The lines at the top of the bars reflect the SEM of the measurements. The numbers above the bars are the p-values (from Inwood and Philp 1973).

unaffected individuals. Analysis by this author of data presented by Beckman and Smith (1972) concerning TEKTITE II aquanauts suggested that a slight (0.25% of red cells) but statistically significant ($p < 0.02$) increase in reticulocyte counts occurred postdive. This was not related to any signs of decompression sickness nor to any evidence of hemoconcentration. Conversely, Hock, Bond, and Mazzone (1966) reported no significant changes in

reticulocyte counts during a HeO_2 saturation dive (SEALAB II). Similarly, Hamilton, MacInnis, Noble, and Schreiner (1966) reported no significant changes in red-cell counts or hemoglobin concentration during a HeO_2 saturation dive to 650 fsw (21.7 ATA). Linaweaver (1969) did not find any significant changes in red-cell counts or hemoglobin concentration either during or after saturation HeO_2 chamber dives. Kemph and Hitchcock (1948) found no significant changes in red-cell morphology or mean corpuscular hemoglobin concentration following explosive decompression of dogs to simulated high altitudes.

Barthélémy (1963) observed an increase in red-cell sodium and a decrease in red-cell potassium in divers breathing air at simulated depths of 30 msw (3.9 ATA) and 60 msw (6.8 ATA). The potassium depletion tended to persist after decompression whereas the sodium returned to normal values. Philp, Inwood, Ackles, and Radomski (1974) found no change in red-cell sodium, as compared to predive values, following decompression after 1 hr at a simulated depth of 100 fsw (4 ATA). Investigations of mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) generally have not revealed changes associated with compression-decompression (Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski 1972; Philp, Inwood, Ackles, and Radomski 1974). Kindwall (1972), however, noted a slight but statistically significant reduction in MCHC in a group of tunnel workers who had been working daily for 1 week at about 3.4 ATA, as compared to a similar group working in free air. Hemoglobin concentration was not significantly different in the two groups. In conjunction with the reduction in MCHC there was a slight but significant increase in MCV. This latter observation is suggestive of a fluid shift into the red cells and this subject will be discussed in greater detail under *Fluid and Electrolyte Shifts.*

Since the pioneer observations of End and Swindle on blood sludging and red-cell aggregation following decompression, several authors have confirmed the existence of this phenomenon. Wagner (1945) noted the passage of sludged red cells through the pial vessels of cats rapidly decompressed from high pressures, as have other investigators using various animal models of DS (Heimbecker, Lemire, Chen, Koven, Leask, and Drucker 1968; Buckles 1968; Wells et al. 1971; Philp et al. 1971). The formation of red-cell aggregates appears to be invariably associated with stasis of flow but the aggregates may persist after flow has been restored. We have observed red-cell fragmentation and deformation (i.e. helmet cells) in association with intravascular bubbles following rapid decompression of rats (Inwood and Philp 1973; Warren et al. 1973).

Collecting blood samples from divers while they are at simulated depth (for subsequent examination at the surface) is fraught with difficulty because a technical error may be introduced by the formation of bubbles during decompression, resulting in hemolysis. Moreover, calculation of MCV, MCH, and MCHC are only as reliable as the initial measurements. Since the counting of red cells by whatever technique involves considerable chance of variation, these values must always be viewed with some suspicion. Nevertheless, existing data suggest that changes in hemoglobin concentration, red-cell size, and reticulocyte numbers are more likely to be encountered when air is the breathing mixture rather than HeO_2. Whether this is related to a greater propensity for bubble formation or to a membrane-related effect of nitrogen (as will be discussed later) remains open to question.

LEUCOCYTES

Kemph and Hitchcock (1948) failed to detect any change in the leucocyte counts of dogs subjected to explosive decompression. Smith and Brown (1951) did an extensive study of

leucoctye changes in normal and splenectomized cats exposed for 30-40 min to simulated high altitude after rapid decompression (36,000 ft in 5 min). They found that acute decompression stress produced a rapid doubling of leucocytes in both normal and splenectomized cats, with increases in eosinophils and neutrophils. Lymphocytes did not change significantly. Leucocytes have been observed adhering to the periphery of intravascular bubbles following the intravenous injection of air into rabbits (Adebahr and Kupffer 1967; Adebahr and Stack 1969; Adebahr 1971) and the rapid decompression of rats from high air pressures (Philp, Inwood, and Warren 1972). Inwood and Philp (1973) used the standardized compressed-air, rat decompression model developed in their laboratory and showed that there were significant increases in the total leucocyte counts of rats moderately or severely affected with DS (see Fig. 8). These increases were due largely to increases in the numbers of polymorphonuclear leucocytes.

Masland (1948) observed leucocytosis in aviators suffering from acute neurological DS. Analysis of TEKTITE II air saturation dives (Beckman and Smith 1972) revealed significant increases in total white-cell and neutrophil counts, after decompression, in three of the six missions reported. The authors felt, however, that these changes were more likely related to skin and ear infections than to decompression stress since previous data collected during TEKTITE I dives did not show changes in leucocytes either during the dive or after decompression. Other investigators have not been able to show significant changes in total leucocytes or differential counts immediately following decompression (Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski 1972) from a simulated air dive or up to 96 hr later (Philp, Inwood, Ackles, and Radomski 1974).

Helium-oxygen saturation dives have yielded conflicting results. Some authors reported no significant changes in leucocytes either during the exposure or thereafter (Linaweaver 1969; Hamilton et al. 1966; Bühlmann et al. 1970). Vorosmarti, Bradley, Linaweaver, Kleckner, and Armstrong (1970) however, found that HeO_2 saturation dives were associated with significant increases in monocyte counts which became evident on the 3rd day of the dive and which persisted for 2 to 3 days postdive. Eosinophil counts became significantly elevated 7 to 8 days postdive. Somewhat earlier, Waldvogel and Bühlmann (1968) observed a marked increase in the leucocyte counts of four divers following a saturation exposure to 23 ATA of HeO_2 (2.5-3.5% O_2) and Bennett and Gray (1971) also observed leucocytosis after a HeO_2 saturation dive. Bonin et al. (1973) saw increased leucocyte numbers in divers following a HeO_2 dive (2 hr at 10 ATA).

To date, no author has proposed a satisfactory explanation for these various changes. In some cases the presence of infection might be responsible, but this cannot account for the leucocytosis in all cases. Animal experiments have indicated that leucocytosis can be observed fairly soon after decompression from high pressures or to simulated high altitude. The variety of gas mixtures and dive profiles used in experiments in which leucocytosis has been observed in man, and the absence of observable leucocytosis in other, similar experiments make it unlikely that hyperoxia or inert gas effects could account for these changes. Bennett (1972) reported that sudden, severe exercise resulted in a significant increase in circulating leucocytes and pointed out that these changes correlated with increases in circulating velocity, which appeared to flush sequestered white cells into the blood. This effect could also occur in response to the hemodynamic changes induced by increased epinephrine output. It is of interest to note that Waldvogel and Bühlmann (1968) saw increased urinary output of epinephrine during the last 24 hr of decompression from a HeO_2 saturation dive. Using two of the same subjects, Bühlmann et al. (1970) observed only a transient increase in urinary catecholamines which occurred shortly after maximum

pressure was obtained. Slight decreases were detected during decompression and no leucocytosis occurred. Urinary catecholamines were not altered following an air dive in which leucocyte counts did not change significantly (Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski 1972).

Thus it is possible that leucocytosis might relate more to the degree of stress, either physical or emotional, experienced by a particular diver than to any other factor. The inconsistencies observed in white cell differential counts could be due to the influence of subclinical infection, the adherence of white cells to *silent* bubbles and their subsequent removal, or to local hemodynamic or cellular influences which might result in the selective washout of certain cell types.

CIRCULATING ENDOTHELIAL CELLS

Philp, Inwood, and Warren (1972) found that the number of free, circulating endothelial cells increased in direct proportion to the severity of DS in afflicted rats. They felt that the isolation of endothelial cells by gas bubbles and capillary stasis probably resulted in cell hypoxia with the subsequent sloughing off of these cells. The authors pointed out that such denuded areas could serve as foci for platelet aggregation and thrombus formation. In electron microscopy studies Warren et al. (1973) found that intravascular bubbles caused pressure damage to endothelial cells which subsequently herniated through fenestrations in the more rigid structures of the arterial wall. Deposits of fibrin were noted on the vessel wall after endothelial damage, as well as layering of platelets over the endothelium.

FLUID AND ELECTROLYTE SHIFTS

Hemoconcentration as indicated by an increase in packed-cell volume (PCV) or by estimates of blood volume has been a frequent observation associated with DS in animals decompressed from high pressures (Carson 1942; Cockett, Nakamura, and Franks 1963; Cockett and Nakamura 1964a; Cockett, Nakamura, and Franks 1965; Philp et al. 1967; Heimbecker et al. 1968; Wells et al. 1971; Inwood and Philp 1973). Similar increases in PCV have also been seen in experimental animals following rapid or explosive decompression to simulated high altitude (Kemph and Hitchcock 1948; Smith and Brown 1951) and the intravenous injection of nitrogen (Hetherington and Miller 1946).

Hemoconcentration has commonly been associated with clinical DS in man (Masland 1948; Malette, Fitzgerald, and Cockett 1961, 1962; Cockett and Nakamura 1964b; Brunner, Frick, and Bühlmann 1964; Barnard, Hanson, Rowton-Lee, Morgan, Polak, and Tidy 1966; McCallum 1968; Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski 1972a; Saumarez, Bolt, and Gregory 1973).

Although changes in PCV have seldom been seen following nonsaturation dives in which no incidence of bends existed (Barthélémy 1963; Philp, Freeman, Francey, and Ackles 1974), a reduction in PCV has been a frequent observation during or after saturation diving. Chouteau (1969) reported a loss of red cells in the CONSHELF I and II projects. A significant reduction in PCV was observed in one of six dive groups in TEKTITE II (Beekman and Smith 1972). In TEKTITE I dives, however, they observed an increase in postdive PCV which they attributed to dehydration. Widell, Pilmanis, Chapman, Pilmanis, and Given (1973) reported that both PCV and hemoglobin concentration decreased significantly during a 7-day sojourn in the HYDRO-LAB habitat located in 50 fsw. The parameters remained depressed for some days postdive. This observation was subsequently

confirmed by Philp, Freeman, Francey, and Ackles (1974) under nearly identical diving conditions.

Blood studies during HeO_2 saturation diving have also yielded conflicting results. Schaefer, Bond, Mazzone, Carey, and Dougherty (1968) saw no significant changes in PCV or hemoglobin concentration during a 12-day saturation at 7 ATA. In the SEALAB II experiments (MacInnis and Bond 1969) red-cell count and PCV fell during the first few days of the saturation dive, with recovery about the 9th day. In a dry-chamber saturation dive to 650 fsw Hamilton et al. (1966) found no significant change in red-cell count, PCV, or hemoglobin concentration during the exposure. No changes were seen in GENESIS E (a dry-chamber saturation dive at about 7.0 ATA) or in SEALAB (an in-sea saturation dive at 6.8 ATA).

In CONSHELF III (Chouteau 1969), carried out at a depth of 328 fsw (11 ATA), no hematological data was included, but a preliminary dry-chamber saturation dive at a similar pressure did not induce any significant change in hematological parameters. Bühlmann et al. (1970) noted a slight fall in PCV following decompression from a saturation dive at 31 ATA. In earlier experiments at 22 ATA (Waldvogel and Bühlmann 1968) no changes in PCV, hemoglobin, or red-cell count were noted during or after the dive. Similarly Vorosmarti et al. (1970) found no significant changes in red-cell count, reticulocyte count, hemoglobin concentration, or PCV during HeO_2 saturation dives (dry-chamber) to 450 fsw (14.6 ATA) although there was a significant reduction in PCV immediately postdive. In a 600 fsw (19.2 ATA) chamber dive, PCV rose on the 3rd day of saturation and fell thereafter to significantly low levels during the decompression phase. Hemoglobin concentration was also depressed significantly in the postdive samples. These authors felt that the repeated blood sampling contributed to this "anemic" response. In an earlier publication (Bradley and Vorosmarti 1968) they reported that a 30-min exposure to 1.9 or 2.8 ATA of pure oxygen caused a depression in PCV and hemoglobin 7 days after the exposure in student divers, but not in experienced ones. They felt that a transient depression or erythropoiesis was the most likely explanation for the response. In a series of saturation dives at pressures ranging from 7 to 19.2 ATA, Linaweaver (1969) found no significant changes in hemoglobin PCV or red-cell counts either during or after the dives.

These frequent observations of reductions in PCV, red-cell count, and hemoglobin concentration during or after saturation dives could be the result of depressed erythropoiesis, increased red-cell destruction, or increased plasma volume (hypervolemia). Should the first two causes pertain, this discussion would rightly belong to the section on red-cell changes. Certainly these possibilities cannot be discounted.

Hyperoxia is known to increase red-cell destruction and may depress erythropoiesis as an adaptive response to the increased oxygen tension in the blood (Mengel, Kann, and Horton 1964; Mengel, Kann, Lewis, and Horton 1964; Mendel, Kann, Smith, and Horton 1964; Mengel, Kann, Heyman, and Metz 1965; Landaw, Leon and Winchell, 1970; Vorosmarti et al. 1970; Widell et al. 1973). Schaefer, Bond, Mazzone, Carey, and Dougherty (1968) and Schaefer, Jacey, Carey, and Mazzone (1968) felt that a PO_2 of 300 mm (0.4 ATA) was probably the threshold for the antihematopoietic effect of O_2. Table 1 summarizes the evidence of reduced PCV, red-cell count, or hemoglobin concentration during or after saturation diving on various gas mixtures and lists the partial pressure of oxygen (insofar as this author could determine) in each situation. There appears to be little relationship between the partial pressure of O_2 in the breathing mixture and the detection of an anemic response either during or after the dive. Rather, the response appears to be associated more frequently with extensive swimming in the sea, especially when air is the breathing gas.

TABLE 1

Summary of hematological data during and after saturation diving*

Project	Total ATA	N_2 ATA	He ATA	O_2 ATA	Days	Swimming	During PCV	During HB	During RBC	After PCV	After HB	After RBC	Reference
CONSHELF I	2.06	1.57	–	0.42	7	in sea			↓			↔	Chouteau (1969)
CHOUTAQUA	12.61	–	12.38(?)	0.23	5	–	↔	↔	↔				Chouteau (1969)
CONSHELF II	1.95	1.56	–	0.39	30	in sea		"discrete anemia"					Chouteau (1969)
CONSHELF III	10.95	0.10	10.62	0.23	30	in sea	↔	↔	↔				Chouteau (1969)
TEKTITE II	2.50	2.00	–	0.50	14-21	in sea				↓	↓	↔	Beckman & Smith (1972)
HYDRO-LAB	2.50	2.00	–	0.50	7	in sea	↓	↓	↓(?)	↓	↓	↓(?)	Widell et al. (1973)
HYDRO-LAB	2.50	2.00	–	0.50	7	in sea				↓	↓	↓(?)	Philp, Freeman, Francey, & Ackles (1974)
GENESIS E	7.00	0.40	6.30	0.27	12	–	↔	↔	↔	↔	↔	↔	Schaefer, Bond, Mazzone, Carey, & Dougherty (1968)
SEA-LAB I	6.80	1.16	5.37	0.27	9	in sea	↔	↔	↔	↔	↔	↔	MacInnis & Bond (1969)
SEA LAB II	7.20	1.30	5.62	0.25-0.35	10-30	in sea	↓	↓	↓	↔	↔	↔	MacInnis & Bond (1969)
MAN-IN-SEA	14.60	0.15	14.02	0.44	1	–				↔	↔	↔	MacInnis & Bond (1969)
MAN-IN-SEA	20.70	–	20.40	0.31	2	–	↔	↔	↔				Hamilton et al. (1966)
	22.00	0.80	21.50	0.56-0.80	2½	–				↔	↔	↔	Waldvogel & Bühlmann (1968)
	31.00†	0.75	29.60	0.43-2.70	3½	wet pot				↓(?)	↔	↔	Bühlmann et al. (1970)
	7.10	1.00	5.80	0.30	9	wet pot	↔	↔	↔	↔	↔	↔	Vorosmarti et al. (1970)
	14.60	1.00	13.30	0.30	9	wet pot	↓	↔	↔	↓	↔	↔	Vorosmarti et al. (1970)
	19.20	?	18.70	0.50	6	–	↔	↔	↔	↔	↔	↔	Linaweaver (1969)
	2.0††	1.60	–	0.40	1½	–	↔	↔	↔	↔	↔	↔	Schaefer, Jacey, Carey, and Mazzone (1968)

*some information in this table was taken from MacInnis, J. B. 1966. The medical and human performance problems of living under the sea. Can. Med. Assoc. J. 95(5):191-200.

† with excursions to 36 ATA †† with excursions to 6 ATA ? indicates data not fully confirmed or not statistically significant

Widell et al. (1973) commented on the known effect of prolonged weightlessness—elimination of the normal gravitational pooling of blood in the lower extremities. This shift of blood to the thoracic organs results in the recruitment of tissue fluid and the subsequent cardiac loading initiates a renal response with increased sodium and water excretion. If the sodium and water loss persists for a sufficient length of time, a true reduction in blood volume may result. Although Widell's group saw increased sodium, potassium, and water excretion and decreased aldosterone output in two of their three subjects, they discounted the effect of weightlessness as an explanation for the reduced red-cell mass. Rather they felt this was due to hyperoxia because cardiovascular and respiratory tests indicated that a blood volume reduction had not occurred. The conditions of the aquanaut, however, differ greatly from those of the astronaut in that the weightlessness is intermittent and of comparatively short duration. The renal response may not persist sufficiently to produce a loss of blood volume and a reduction in red-cell count, hemoglobin concentration, or PCV may thus reflect hemodilution rather than a true loss of cell mass.

Changes in blood and urine electrolytes have likewise been observed in nonsaturation diving conditions. In discussing a statistically significant reduction in serum sodium concentrations in subjects with decompression-related signs and symptoms after a 10-min sojourn at a simulated depth of 300 fsw (10.3 ATA) Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski (1972) speculated (in the absence of clear evidence of sodium diuresis) that sodium was passing from the extracellular space to some intracellular site. They noted that disturbances in normal cell metabolism interfered with the sodium pump mechanism, resulting in intracellular accumulation of sodium. This has been

seen in a number of pathological situations including uremia and shock (Welt, Smith, Dunn, Czerwinski, Proctor, Cole, Balfe, and Gitelman 1967; Cunningham, Wagner, and Shires 1970).

Barthélémy (1963) also noted a reduction in plasma sodium which occurred in divers under pressure and persisted after decompression. Linaweaver (1969) did not observe significant changes in serum electrolytes during or after HeO_2 saturation diving and Bühlmann et al. (1970) noted no significant changes in serum electrolytes after a saturation exposure to 31 ATA, although renal excretion of sodium, calcium, magnesium, and chloride decreased. Radomski and Bennett (1970) observed a significant reduction in urinary sodium and calcium after 30 min at 10.3 ATA in air, as well as significant increases in serum potassium and phosphorus, with a return to normal values within a few hours. These changes were not seen when helium-oxygen was breathed in the same dive profile. No significant changes in serum sodium were observed. These authors attributed the effects to the presence of nitrogen and noted the similarity to electrolyte shifts observed with various anesthetic agents. Schaefer, Bond, Mazzone, Carey, and Dougherty (1968) noted transitory increases in urine sodium, potassium, and chloride during a 12-day HeO_2 dive at 7 ATA. Albano (1970) also saw increased urinary output of sodium and, more particularly, of potassium during an exposure to high pressure (9 ATA). Bennett and Hayward (1967) found significant decreases in the sodium levels of cerebral spinal fluid of cats exposed to 10 ATA of nitrogen-oxygen or argon-oxygen but not helium-oxygen. Bennett (1968) hypothesized that nitrogen at high pressure might interfere with the membrane sodium pump mechanism leading to the intracellular accumulation of sodium. It is of interest to note that chlorpromazine, one of the first drugs reported to offer protection against experimental decompression sickness in animals, is known to have a membrane-stabilizing effect and thus to protect red cells from hypotonic hemolysis (Seeman 1966; Seeman and Weinstein 1966; Seeman, Sha'afi, Galey, and Solomon 1970).

BLOOD CHEMISTRY

ENZYMES

The knowledge that numerous pathological states induce cell damage and the release of intracellular isoenzymes into the blood prompted the study of these enzymes in hyperbaric experiments to determine whether hyperoxia and/or decompression induced sufficient cell damage to yield detectable increases in blood enzyme levels. As with many of the parameters discussed thus far, the results to date have been somewhat equivocal.

Barthélémy (1963) did not find any significant changes in plasma or corpuscular cholinesterases following short exposures to either 30 or 60 msw (3.9-6.8 ATA) when divers breathed air. Philp, Inwood, Ackles, and Radomski (1974) reported that serum cholinesterase activity was depressed upon decompression, and for 3 days after a 10-min chamber dive (air) to 10 ATA. Creatinine phosphokinase (CPK) levels tended to be depressed postdive and lactic acid dehydrogenase (LDH) and glutamic oxaloacetic transaminase (GOT) levels were significantly depressed 24-72 hr later. These changes were largely prevented by the antiplatelet drug VK744, and the authors speculated that the decline, especially in LDH and GOT, might be related to the observed loss of platelets since these enzymes occur in platelets (Zucker and Borelli 1958). Previously Martin, Gray, and Nichols (1973), using a 1-hr exposure to 4 ATA air, reported that newly trained divers demonstrated significant increases in alkaline phosphatase (AlPh) and aspartate aminotransferase (AsAm) during the dive whereas untrained subjects did not. Some subjects in both groups, however, showed elevated CPK levels up to 3 days postdive but the trained subjects also showed elevated predive levels.

Kindwall (1972) did not observe any significant difference in CPK levels between tunnelers working in free air as opposed to those working at pressure of 35-38 psi (3.6 ATA).

Studies of air saturation dives have also revealed minor changes in blood enzyme levels. Schaefer, Jacey, Carey, and Mazzone (1968) found that a 36-hr air saturation dive at 2 ATA with excursions to 6.0 ATA did not produce any significant changes in serum GOT or glutamic-pyruvic transaminase (GPT) either during the dive or within 3 hours of surfacing. LDH, however, rose during and after the excursions to 6 ATA. The authors felt that this response was to some extent related to circadian rhythms of LDH activity since it occurred only when the excursion took place at 1200 hr. In a subsequent publication (Jacey and Schaefer 1968) these authors demonstrated a circadian cycle for LDH with peak activity in plasma occurring between 1200 and 2400 hr. High-pressure stress (no-decompression dive to 5 ATA) elicited increased plasma LDH activity only when applied during the descending phase of the normal circadian cycle.

Studies of the TEKTITE II missions (Beckman and Smith 1972) revealed significant postdive increases in LDH and GOT, which the authors felt were due to cell destruction. Conversely, in HYDRO-LAB air saturation dives, slight, but statistically significant postdive decreases in AlPh, CPK, and LDH were observed which may have been due to hemodilution or to platelet loss (Philp, Freeman, Francey, and Ackles 1974).

Helium-oxygen saturation diving has been the subject of much research relating to blood isoenzyme patterns. Bennett and Gray (1971) found that no significant changes occurred in levels of several enzymes (LDH, AsAm, AlPh, alpha hydroxybutyrate dehydrogenase [HBD] and LDH-HBD ratios) following a HeO_2 dive to 1500 fsw (46.5 ATA). Waldvogel and Bühlmann (1968) reported a slight increase in CPK in subjects exposed to 22 ATA of HeO_2 for 60+ hr. SEALAB II data revealed significant increases in GOT and LDH during the dive (MacInnis and Bond 1969). Commenting on a series of HeO_2 saturation dives at a variety of pressures, Linaweaver (1969) noted no significant changes in AlPh, GOT, GPT, or LDH levels in serum. In one 600-fsw dive (19.2 ATA) there was an increase in the proportion of heart LDH isoenzyme but GOT was normal, indicating that tissue damage had not occurred. Bühlmann et al. (1970) measured a variety of isoenzymes before and after an 81-hr saturation dive at 31 ATA with excursions to 36 ATA. In comparing the results before and after the trial, they found no significant change in AlPh, slight increases in LDH and HBD with varying ratios in each subject, and a decrease in AsAm.

Existing evidence suggests that neither the degree of hyperoxia commonly encountered in saturation diving nor the effects of *safe* decompression induces enough tissue damage to cause significant increases in blood isoenzyme levels. Enzyme levels could, of course, be elevated by the physical exertion of diving since this effect of exercise is well-documented (Schlang and Kirkpatrick 1961; Halonen and Koltinen 1962; Nuttall and Jones 1968; Refsum, Schomm, and Tveit, 1972). Martin and Nichols (1974) noted elevated CPK levels in the early stages of diver training with a return toward normal after 6 weeks. The effect was more pronounced in winter than in summer, suggesting to them that cold stress exaggerates the response. These authors felt that the CPK response might be a useful indicator of an individual's degree of adaptation to the hyperbaric environment, but others (Nuttall and Jones 1968) pointed out that physical conditioning influences the degree of elevation of this and other isoenzymes in serum. As indicated above, the existence of several of these enzymes in blood platelets could also influence serum measurements if the platelet count should change significantly during an experiment.

Information about blood enzyme changes in overt DS is scanty. Stegal and Smith (1972) noted marked increases in CPK levels after both fast and slow decompression of miniature

swine whereas LDH levels fell in the same samples. These authors also found laboratory evidence of disseminated intravascular coagulation. Using the treadmill test devised by Philp and Gowdey (1962), Powell (1973) decompressed rats, rabbits, and guinea pigs and correlated elevations in serum isoenzymes with the severity of DS. In the absence of overt signs of DS, no elevation of enzymes was observed. LDH and CPK levels tended to rise in less severely affected animals and severe DS was accompanied by rises in GOT and GPT. The authors felt the pattern was indicative of myocardial damage. Using a similar approach Freeman and Philp (1974) found increases in LDH and GOT levels in moderately affected rats 24 hr after decompression and severely affected animals showed even greater levels of these enzymes. The results of assays performed immediately after decompression were equivocal, suggesting that blood isoenzyme assays may be of greatest clinical use in cases of DS where the onset of symptoms is delayed.

This delay in the rise of blood isoenzyme levels has been observed in other pathological states. Coodley (1966) pointed out that GOT levels in serum do not peak for 24-48 hr after myocardial infarction, with increases in LDH being delayed even more. In his opinion, the HBD isoenzyme form of LDH is more specific for infarction and HBD-LDH levels more useful than total LDH activity. He also found that increased CPK levels were highly specific for myocardial infarction 12-72 hr after the event, provided that the patient was euthyroid and that no brain damage or skeletal muscle disease was present. Authorities in this field generally agree that the absolute increases in blood isoenzyme levels correlate well with the extent of tissue damage, that the temporal factor is important and varies from one enzyme to another, and that the pattern of enzyme changes is dependent upon the organ incurring the injury (Wroblewski 1958; Kibe and Nilsson 1967; Ramsey, Yap, and Spector 1968; Nerenberg and Pogojeff 1969). The infusion of norepinephrine into anesthetized dogs has been shown to increase circulating levels of GOT and this response can be blocked by adrenergic blocking drugs (Loegering and Critz 1968). Nonspecific stress responses undoubtedly affect isoenzyme levels in divers and complicate the interpretation of data.

CATECHOLAMINES AND CORTICOSTEROIDS

Evidence from human diving and decompression experiments suggests that a stress response is not uncommon. Elevations in blood and urine levels of catecholamines and corticosteroids and their metabolites during compression and during or after decompression have been demonstrated by several authors (Schaefer, Bond, Mazzone, Carey, and Dougherty 1968; Chouteau 1969; MacInnis and Bond 1969; Bühlmann et al. 1970; Waldvogel and Bühlmann 1968; Bennett and Gray 1971). Decreases in blood cortisol levels have also been reported during compression (Chouteau 1969) and following decompression (Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski 1972; Beckman and Smith 1972; Martin et al. 1973). These reductions have been attributed variously to increased utilization as an extension of the stress reaction or to decreased output because of blockage of the capillary microcirculation of the adrenals by bubbles. Gersh and Catchpole (1946) demonstrated bubble formation in the adrenal cortex of decompressed rabbits.

Lambertsen (1968) pointed out that DS constitutes a form of stress resulting in the increased output of catecholamines from the adrenal medulla and he elaborated on the hemodynamic consequences and their significance in DS. Existing evidence indicates that diving and/or compression-decompression may cause increased catecholamine output in the absence of DS. This may initiate a complex sequence of events. In addition to elevating free fatty acid (FFA) levels, (see following section) catecholamines may increase Factor VIII

activity (Nour–Eldin 1967), increase clotting activity, shorten platelet half-life (Ozge, Mustard, Hegardt, Rowsell, and Downie 1963) and perhaps predispose to thrombus formation (Ozge et al. 1963; Rowsell, Hegardt, Downie, and Mustard 1966). Catecholamines have been shown to aggregate platelets in vitro (Clayton and Cross 1963; Mills and Roberts 1967b). As discussed previously, catecholamines may also elevate blood isoenzyme levels. Most of these effects may also be triggered by elevated plasma lipid levels, and a complex interaction between these two factors undoubtedly exists.

PLASMA LIPIDS

Ever since Vernon (1907) observed that gaseous nitrogen was 5.3 times more soluble in fats than in water, considerable attention has been given to the possible influence of body lipids in the etiology of decompression sickness. Most of the early work centered on the role of storage fat depots as nitrogen reservoirs. It was not until 1945 that Berg, Harris, Whittaker, and Twitty recognized the possible significance of plasma lipids. Because their experiments in vitro showed that hydrophobic surfaces such as lanolin and paraffin retained minute air films which acted as nuclei for bubble growth, they suspected that a similar phenomenon might occur in vivo. Studies with hyperlipemic animals, however, failed to yield supporting evidence for this hypothesis.

Interest in plasma lipids was renewed when it was found that fat embolism was a not-uncommon post-mortem finding in human fatalities from DS, particularly following decompression to high altitudes (Haymaker and Davison 1950; Haymaker and Johnston 1955). Haymaker, Johnston, and Downey (1956) reported two fatalities after high-altitude flying. Both victims had histopathological evidence of extensive fat embolism and both had a patent *foramen ovale*. The authors also noted "intense generalized lipemia" and pointed out that the patent *foramen ovale* would permit the entry of venous gas bubbles, which otherwise would be filtered out by the lungs, into the left side of the heart, and hence reach the brain and other vital organs. The same would, of course, be true for lipid emboli. Subsequently, laboratory experiments confirmed the presence of fat emboli in various organs and tissues in animals with severe DS (Clay 1963; Cockett et al. 1965).

Barthélémy (1963), in commenting on the ameliorative action of heparin in both experimental and clinical DS, speculated that some of this benefit might derive from the known lipemia-clearing action of the drug. Our laboratory (Philp 1964) found that anticoagulation with coumarins did not afford significant protection against DS in rats whereas an experimental antilipemic agent did so, thus providing supporting evidence for Barthélémy's suggestion. Further studies in our laboratory, using the rat-treadmill decompression test, demonstrated that susceptibility to DS was increased following alimentary lipemia. Severity was related to plasma lipid levels, with the paradoxical exception of severely afflicted animals, in which there was a marked reduction in circulation lipids (Philp et al. 1967). We postulated that intravascular bubbles triggered the aggregation of platelets and that coalesced plasma lipids became incorporated into such aggregates. The involvement of lipids in clinical thrombi has been noted (Mustard, Murphy, Rowsell, and Downie 1964.) The absence of a significant shift in the gas chromatography spectrum of neutral lipids or phospholipids following DS supported our hypothesis that the reduction in total plasma lipids was a physical, rather than biochemical, phenomenon (Clark, Philp, and Gowdey 1969a). Previously, lipid emboli associated with clinical or experimental DS had been thought to derive from bone marrow fat or lipid depots. Kalberer (1969) demonstrated no difference in the extent of lipid emboli in the lungs of thin mice with DS as compared to obese litter-mates, nor were they able to correlate the severity of DS with the degree of lipid embolization. Earlier Reidbord (1967) found no difference in the incidence of pulmonary

fat emboli between rabbits fed a normal diet, those fed a high cholesterol diet, and those with fatty livers induced by treatment with ethionine. Hartveit, Lystad, and Minken (1968) saw fat emboli in the right ventricle, coronary arteries, and kidneys of rabbits and mice following the rapid intravenous injection of air, further indicating that the source of such emboli is unlikely to be tissue fat. Pauley and Cockett (1970) felt that the coalescence of plasma lipids was the most likely source of fat emboli. Our laboratory recently obtained electron microscopic evidence that lipid particles become incorporated at the gas-liquid interface of intravascular bubbles produced in rats by rapid decompression (Philp, Inwood, and Warren 1972; Warren, Philp, and Inwood 1973). The trapping of such thrombi, composed of bubbles, platelets, and lipids, would explain the disappearance of plasma lipids from the circulating blood which we observed previously in rats severely affected with DS.

Changes in plasma lipid levels in man have been observed both in chamber dives and in open-water dives. Radomski and Bennett (1970) recorded moderate but statistically significant decreases in FFA and cholesterol levels during a 30-min HeO_2 chamber dive to 200 fsw (7.1 ATA), whereas Waldvogel and Bühlmann (1968) did not see any clear-cut changes in cholesterol levels of two subjects following a HeO_2 saturation dive at 21-22 ATA. Philp, Ackles, Inwood, Livingstone, Achimastos, Binns-Smith, and Radomski (1972) showed slight but statistically significant increases in serum FFA levels in subjects after a 10-min exposure to 10.1 ATA (air). The TEKTITE II missions (Beckman and Smith 1972) did not appear to elicit any significant postdive changes of cholesterol levels in the divers. Philp, Inwood, Ackles, and Radomski (1974) obtained evidence of postdive elevations in FFA after a 1-hr chamber air dive to 4 ATA. Martin et al. (1973) reported similar postdive increases in FFA levels using the same dive profile. Triglyceride and cholesterol levels remained unchanged. Air saturation dives (2.5 ATA) in the HYDRO-LAB habitat showed a slight but progressive reduction in FFA and cholesterol values for 2-3 days postdive (Philp, Freeman, Francey, and Ackles 1974). Changes in FFA levels appear to have been encountered more commonly in divers than changes in cholesterol or triglycerides. Since catecholamines have been shown to elicit a lipolytic effect with elevation in serum FFA's (Gordon and Cherkes 1956; White and Engel 1958; Mayer, Moran, and Fain 1961; Burns and Colville 1962), such postdive increases probably represent a generalized stress response.

Elevated plasma lipids have been shown experimentally to accelerate blood clotting (MacFarlane, Trevan, and Attwood 1941; Fullerton, Davie, and Anastasopoulos 1953; Poole 1955; O'Brien 1957; McDonald and Edgill 1958; Margolis 1962), favor experimental thrombogenesis (Thomas and Hartroft 1959; Gresham and Howard 1960; Connor and Poole 1961; Mustard, Murphy, Rowsell, and Downie 1962; Connor, Hoak, and Warner 1963; Hoak 1964; Born and Philp 1965; Warner, Hoak, and Connor 1967), increase platelet adhesiveness (Cullen and Swank 1954; McDonald and Edgill 1958; Hellem 1960; Kerr, Pirrie, MacAulay, and Bronte-Stewart 1965; Philp and Wright 1965), precipitate red cell and platelet aggregation in vivo (Thompson, Williams, and Walters 1969), reduce the circulating platelet count (Loughry and Cole 1954; Meng, Cress, and Youmans 1958; Philp and Wright 1965), and aggregate platelets in vitro (Haslam 1964; Kerr et al. 1965; Farbiszewski, Skrzydlewski, and Worowski 1969). In the light of these observations it is small wonder that elevated lipid levels increase the incidence and severity of experimental DS and it would seem reasonable to assume that plasma lipids play a significant role in the etiology of clinical DS.

PLASMA PROTEINS

Although changes in plasma proteins have been reported in association with compression-decompression, the results have been equivocal and difficult to interpret. Radomski and Bennett (1970) found significant decreases in albumin and total protein levels following

decompression from 10 ATA HeO_2 and felt this to be due to increased capillary permeability and fluid shifts. Conversely, Beckman and Smith (1972) found slight but statistically significant increases in total plasma protein in two groups of TEKTITE II divers, which probably reflected the state of hydration at the time. These authors also found increases in angiotensin I and unexplained increases in immunoreactive proteins. Other investigators (Waldvogel and Bühlmann 1968; Bühlmann et al. 1970; Philp, Inwood, Ackles, and Radomski 1974) were unable to find significant shifts in albumin or total proteins following a variety of compression-decompression profiles. Earlier, Smith and Brown (1951) reported significant increases in the total plasma proteins of cats decompressed to simulated high altitude. Because PCV decreased, they did not believe this to reflect hemoconcentration but rather felt that it might be due to the release of stored protein. It is most likely, however, that changes observed in man are secondary to fluid shifts. It is of interest to note that Bove, Hallenbeck, and Elliott (1974) found that Cr^{51}-labeled red cells proved a more reliable indicator of fluid shifts in dogs with bends than did I^{125}-labeled albumin. These authors found that limb bends were not associated with hemoconcentration whereas paralyzed dogs showed loss of plasma.

DRUGS AND DECOMPRESSION SICKNESS

Early investigations on the effects of drugs on DS were aimed at the alleviation or prevention of joint pain in high-altitude aviators. A number of WW II military reports on this subject were reviewed by Adler (1964). A variety of narcotic and nonnarcotic drugs, including aspirin, were tried without notable success. In one report, dextroamphetamine significantly reduced the incidence of incapacitating bends, but other workers were unable to confirm this observation. Aminophylline was claimed to reduce the incidence and severity of bends at altitude. Subsequently other workers (Campbell and Spencer 1969) showed that theophylline administered to guinea pigs by means of a nebulizer offered protection against DS. Williams, Lyons, Bridge, and Cook (1946), however, did not find that aminophylline provided any significant protection against DS for subjects decompressed to simulated high altitude, nor did analgesics, including aspirin, but other authors (Smith 1946; Wünsche 1958) reported that narcotics and sedatives did reduce the severity of DS somewhat. Lyle and Dahl (1961) reported that protection against DS was afforded to experimental animals by various local and general anesthetics and autonomic depressants. Bennett (1972) reviewed much of the current work relating to the use of pharmacological agents in diving.

The pioneer work of the French regarding the protective action of chlorpromazine and heparin has already been discussed. Our laboratory (Philp 1964) later confirmed that heparin reduced the incidence and severity of DS in rats and showed that an experimental antilipemic agent (partially depolymerized hyaluronic acid) had similar properties whereas coumarin anticoagulants did not. Hartveit et al. (1968) found that prior heparinization improved the survival of rapidly decompressed mice. Campbell and Ward (1968) reported that heparin and papaverine, administered to guinea pigs by nebulizer, afforded protection against DS whereas Reeves and Workman (1971) were unable to find any prophylactic or therapeutic benefit of heparin against DS in dogs. More recently McCormick, Philbrick, Holland, and Harrill (1973) measured cochlear potential function in guinea pigs and found a reduction associated with DS. This loss of function was prevented by heparin. These authors felt that the loss of function, and possibly the sudden onset of deafness sometimes seen in divers following decompression, might be related to a microthrombotic syndrome.

More recent work in our laboratory (Inwood and Philp 1973), using the rat decompression model, found that both heparin and dicumarol provided apparent but not

statistically significant protection against DS. Highly significant reductions in morbidity and mortality were obtained with an experimental antiplatelet agent (VK774, Pharma Research Canada Ltd.), an experimental drug which has antiplatelet and anti-blood sludging properties (polyoxalkol, Cutter Laboratories), and the drug Arvin (Twyford Laboratories) which converts fibrinogen to an unclottable derivative. Drugs which inhibit the fibrinolytic process (epsilon aminocaproic acid, Amicar, Lederle; Trasylol, Bayer) caused statistically significant increases in morbidity and mortality and the analgesics apsirin and indomethacin had no effect. Bennett and Brock (1969) also failed to detect any beneficial effect of aspirin in experimental DS. Ehm et al. (1971) and Schimpf, Piechotta, Ehm, and Fritsch (1971) reported that both Trasylol and heparin afforded protection against DS to decompressed rabbits and dogs. This observation is difficult to reconcile with the effect of Trasylol on the clotting system. Nevertheless Fasciani (1970) used Trasylol both systemically and by intra-articular injection in divers with Type I and Type II bends and reported that it accelerated recovery when used in conjunction with recompression and oxygen therapy. He appeared to attribute these beneficial actions to a general proteolytic activity of the drug.

Many drugs have been shown experimentally to increase the incidence and severity of bends. These include carbachol, doriden (glutethimide), phenacetin (acetophenetidin), epinephrine, leptazol (pentylenetetrazol), megimide (bemegride) and hyoscine (Bennett and Brock 1969), serotonin (Clark, Philp, and Gowdey 1969b) and bradykinin (Chryssanthou, Kalberer, Kooperstein, and Antapol 1964). These last authors also reported that bradykinin antagonists reduced the incidence of DS in mice. Further, they have identified a humoral substance which they have named Smooth-Muscle Activating Factor (SMAF) (Chryssanthou, Teichner, Golstein, Kalberer, and Antapol 1970) which, when injected into mice, will increase their susceptibility to DS and which can be antagonized by certain bradykinin antagonists (Chryssanthou, Kalberer, Kooperstein, and Anatapol 1971). The possible involvement of bradykinin in the pathophysiology of DS might provide an explanation for the apparently controversial results which have been obtained with the drug Trasylol. It has been shown that Trasylol is capable of inhibiting a variety of protease enzymes including kallikrein, which liberates kinins from precursors, and some enzymes involved in the early stages of the coagulation process (Haberland 1970). Thus, whether Trasylol demonstrates beneficial or detrimental effects might well depend upon the extent of involvement of the clotting system in a given situation. If fibrin formation is proceeding actively, Trasylol could have adverse effects by inhibiting fibrinolysis. At an earlier stage, the antibradykinin activity might be beneficial provided that the rate of fibrin production is minimal. Trasylol has been shown to relieve morphine-resistant myocardial pain and this effect is thought to be due to its inhibitory action on kallikrein (Sicuteri, Del Bianco, and Faniciullaia 1970).

Malette, Fitzgerald, and Eiseman (1960), reporting on the protective effects of the surfactant methylsiloxone (Antifoam A, Dow-Corning) against DS in rapidly decompressed rats, were the first to draw attention to the formation of a coagulavelum, or envelope around intravascular bubbles, and thought that the beneficial effects of methylsiloxone were in some way related to this coagulavelum. Subsequently, work in our laboratory indicated that this envelope consists of plasma proteins, lipids, and aggregated platelets (Philp, Inwood, and Warren 1972; Warren et al. 1973). Experiments in our laboratory with antiplatelet drugs related to the coronary vasodilator agent dipyridamole (Persantine, Ciba-Geigy) indicated that such agents were capable of affording protection against DS in rats and, moreover, there was a direct relationship between their potency as inhibitors of aggregation and their effectiveness in protecting against bends (Inwood and Philp 1973). Dipyridamole itself is a very weak inhibitor of aggregation (Philp, Francey, and McElroy 1973) and afforded no

protection against DS in rats (Clark et al. 1969b), whereas more potent derivatives (RA255, VK774, VK744) afforded significant protection (Inwood and Philp 1973). Recently (Philp, Inwood, Ackles, and Radomski 1974) we reported that two of these agents (RA255 and VK744), when administered to volunteers before and after a simulated dive, significantly reduced the postdive loss of circulating platelets which occurred in placebo-treated control subjects. Inhibition of platelet function tests was also observed in the drug-treated groups.

The replacement of fluids in severe DS by plasma expanders such as dextran-40, as originally advocated by Cockett and Nakamura (1964a,b) would now appear to be a well-established practice. Saumarez et al. (1973) claimed to have successfully treated a case of Type II bends, without recompression, using dextran-40, heparin, and aminophylline. Hemoconcentration and some depression of platelets were evident. It is conceivable that some of the benefits of dextran-40 might derive from the fact that it also inhibits platelet adhesion and aggregation (Bygdeman and Eliasson 1967). Most drugs which have been shown to have a beneficial effect in experimental DS have, in fact, some antiplatelet activity as well. In addition to the dipyridamole derivatives and dextran-40 these include chlorpromazine (Mills and Roberts 1967a; Bounameaux 1971; Mason, Read, Saba, and Shermer 1972; Brinson 1973), heparin (Besterman and Gillett 1972), local anesthetics (Aledort and Niemetz 1968; Deutsch, Lechner, Moser, and Stockinger 1971; Mason et al. 1972), aminophylline (Brinson 1972) and theophylline (Ball, Brereton, Fulwood, Ireland, and Yates 1970; Cole, Robison, and Hartmann 1970; Bounameaux 1971; Mason et al. 1972). While it would be naive to suggest that these all worked via the inhibition of platelet aggregation, it may well be that some common property is involved. The notable failure of aspirin, a well-documented inhibitor of platelet function, to alleviate experimental or clinical DS, may be related to the fact that aspirin, although it inhibits the release reaction of platelet constituents, is not an inhibitor of primary platelet aggregation.

General supportive therapy will not be discussed in detail, but some mention should be made of the possible application of high doses of corticosteroids in cases of DS involving severe circulatory shock. The benefits of this therapeutic approach have been demonstrated in the treatment of clinical shock and probably relate to the dilating action of corticosteroids on post-capillary sphincters with improved venous return as the consequence (Lillehei, Longerbeam, Block, and Manax 1964; Lefer and Verrier 1970; Moran 1970).

SUMMARY

Diving, especially saturation diving, entails manifold stress factors which can influence the formed and chemical elements of the blood. These may include physical stress, psychological stress, weightlessness, dehydration, hypothermia, hyperoxia, inert gas effects, and the production of bubbles during decompression. The changes wrought by these factors do not necessarily operate in the same direction, thus it is not surprising that the interpretation of physiological data collected in diving experiments is fraught with difficulties, particularly in view of their often subtle nature. Nevertheless, an assessment of available information permits some tentative conclusions to be drawn.

The generalized stress response probably accounts for many of the observed changes including elevations of blood catecholamines, FFAs, isoenzymes, leucocytes, and cortisol. In this author's opinion, the partial pressures of oxygen which have been utilized in saturation diving do not appear to be correlated with the elevated isoenzyme levels, suggesting that there is not associated tissue damage. Similarly, the reduction in red-cell count which has been observed frequently in connection with saturation diving appears to correlate better with the occurrence of swimming activity than with oxygen tension and may be related to

intermittent weightlessness and fluid shifts or to some unidentified effect, rather than to suppression of erythropoiesis by hyperoxia.

There appears to be a more substantial relationship between decompression, particularly hazardous decompression, and the observations of thrombocytopenia, increased fibrin formation, and hemoconcentration. It now appears highly likely that most decompressions from any significant depth are accompanied by some degree of bubble formation and the occurrence of DS is probably dependent upon the size, frequency, and location of the bubbles. Evidence from animal experiments strongly indicates that the blood reacts to the intravascular bubble in the same fashion as it would to any other foreign surface. A layer of protein, probably fibrinogen in the main, is deposited at the blood-bubble interface as are coalesced plasma lipids. The protein molecules, oriented with their hydrophilic moieties toward the plasma, present a thrombogenic surface which attracts platelets. This leads, in extreme situations, to platelet aggregation and the release of clotting agents such as platelet phospholipid. This bubble membrane may be stripped off to serve as a locus for additional platelet aggregation. These effects, together with stasis of the blood in occluded vessels, may activate the fibrin clotting system. Experiments with human subjects suggest that the process is occurring, at a much reduced level, even after decompressions which induce no clinical signs of DS. The hemoconcentration which has been observed frequently in association with severe DS is thus likely due to the extravasation of fluid as is commonly encountered in stagnant shock, particularly when disseminated intravascular coagulation is a complication. The incorporation of plasma lipids into microthrombi has been noted and would account for the reduction of plasma lipid levels which has been observed in experimental DS and, to a lesser extent, following decompression of human subjects. The occurrence of lipid emboli in severe DS is well documented and also could be related to the coalescence of plasma lipids. A complex interrelationship also exists between plasma lipids, platelet adhesiveness, and the blood clotting system.

The extent to which these reactions occur would be dependent upon the total surface area of gas which is in contact with blood. Bubble size may be an important factor in determining whether or not changes in platelets and clotting factors will be detected. For example, 10 cc of a gas, if present as bubbles of 100μ diameter, would present a total surface area of approximately 0.6m^2. The same volume of gas, existing as bubbles of only 10μ diameter, would have a total surface area of 6.0m^2. Thus, multiple small bubbles may involve a greater risk of activation of the clotting system than a few, large gas emboli. Some preliminary evidence suggests that the state of an individual's platelet population may have a bearing on the degree of platelet loss, a high percentage of extremely reactive platelets leading to increased loss, and a mild platelet defect having the opposite effect. There is evidence that the most active platelets are removed preferentially from the circulation. Adjunctive therapy for severe DS, when indicated, should thus be directed toward expansion of plasma volume and the inhibition of platelet adhesion and aggregation by platelet-inhibiting drugs. Since dextran-40 possesses both of these attributes, it is currently the agent of choice. Antithrombotic drugs of the future may prove useful prophylactically, especially if the problem of hyperbaric osteonecrosis is proven to have a microthrombotic basis.

Far too little information is available concerning changes in blood isoenzymes, electrolytes, catecholamines, cortisol, etc. in clinical DS. This information must be accumulated in order to evaluate the prognostic and diagnostic usefulness of these tests. Existing information indicates, however, that even a moderately elevated PCV or a slightly depressed platelet count ought to be viewed as an indication for adjunctive therapy.

During the preparation of this manuscript the Government of Canada announced, in the Speech from the Throne opening the spring session of Parliament, that, as part of a reorganization of research granting in this country, the Defence Research Board of Canada would cease to exist as a granting body. This agency has provided continuous research funding to our laboratory since 1962. It is the author's hope that this review will be regarded as a modest, farewell tribute to the agency which has served the field of hyperbaric physiology so well for so many years.

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THE TREATMENT OF DECOMPRESSION SICKNESS: AN ANALYSIS OF ONE HUNDRED AND THIRTEEN CASES*

O. E. VAN DER AUE,[1] G. J. DUFFNER,[2] AND A. R. BEHNKE[3]

From the Experimental Diving Unit, U. S. Naval Gun Factory, Washington, D. C. and the Naval Medical Research Institute, National Naval Medical Center, Bethesda, Maryland

BACKGROUND

THE prime objective in the treatment of decompression sickness is the rapid restoration of normal blood supply by immediate recompression which serves to reduce the size of gas emboli and of bubbles in tissues in proportion to the amount of pressure applied. The principles of recompression and the employment of oxygen have long been known but the formulation of specific procedures with reference to symptomatology only recently has been accomplished. As a result of experiments conducted at the Harvard School of Public Health (1) and of the cumulative experience gained during the past ten years at the Experimental Diving Unit, U. S. Naval Gun Factory, Washington, D. C. (2, 3, 4), it has been possible to incorporate three basic principles underlying treatment into a comprehensive tabular outline that has served recently as a guide in the treatment of 113 divers who developed decompression sickness. These principles are: (a) the limitation of the maximal pressure applied during recompression to 65 pounds per square inch gage (165 feet) and the maintenance of this pressure for periods of at least thirty minutes or for as long as two hours, (b) prolonged recompression for periods of twelve to twenty-four hours or longer at pressure levels equivalent to depths between 30 and 60 feet, and (c) the inhalation of oxygen at pressure levels equivalent to 60 feet or less in order to promote the more rapid elimination of nitrogen. The rationale of these principles and their incorporation into a specific treatment outline will be analyzed in relation to their application in the treatment of 113 divers.

It is known that the size of a bubble decreases upon application of pressure in accordance with Boyle's law (5). At a pressure of four atmospheres absolute, equivalent to a diving depth of 100 feet, the volume of a bubble will be reduced 75 per cent compared with its volume at sea level. At a pressure of six atmospheres absolute, equivalent to a diving depth of 165 feet, the volume of a bubble will be decreased 83 per cent. Recompression beyond 165 feet is of little value in reducing bubble size (Fig. 1). It is, therefore, not advisable to recompress a patient beyond this depth as greater pressure only serves to increase the nitrogen content of the tissues without appreciably decreasing the size of the bubbles. Experience has shown that it is better to wait for a period of thirty minutes to two hours at a depth of 165 feet for relief

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The term "decompression sickness" includes compressed air illness, caisson disease and symptoms which persist following too rapid decompression at high altitude.

[1] Captain, (MC) U. S. Navy, Washington, D. C.
[2] Lt. Comdr., (MC) U. S. Navy
[3] Captain, (MC) U. S. Navy, Bethesda, Md.

of symptoms rather than to recompress the patient for relatively short periods at greater depths.

With regard to prolonged recompression, it has been observed that patients with serious manifestations of decompression sickness, and those who did not respond to the usual treatment, did best when kept under a pressure of at least two atmospheres (33 feet) for long periods of time. Under these conditions the patient is able to sleep and adequate time is given for the absorption or elimination of the compressed bubbles. The fact that on previous occasions it frequently has been necessary to recompress patients two and even three or more times in the treatment of bends demonstrates the slowness of bubble absorption or removal. It is stressed that any involvement of the central nervous system makes prolonged exposure to compressed air mandatory.

Prolonged exposure to pressure equivalent to a depth of 33 feet is optimal if the patient's symptoms are absent at this depth. Boycott, Damant, and Haldane (6) and more recently investigators at the Experimental Diving Unit have demonstrated that exposures of twelve to twenty-four hours at 33 feet could be followed by minimal decompression, i.e., less than one minute, without the occurrence of symptoms. At this depth the nitrogen content of the body will not be increased to a level that requires decompression and the volumes of any bubbles present will still be reduced to 50 per cent of their volume at sea level pressure.

The rationale of oxygen therapy in rapidly freeing the circulating blood of bubbles especially for the relief of asphyxia (chokes) was pointed out by Paul Bert (7) and confirmed by Heller, Mager, and von Schrotter (8). The limitation upon the use of oxygen however, is its toxicity. In the resting individual, symptoms of oxygen poisoning rarely occur during a two-hour period of exposure at a pressure equivalent to a depth of 60 feet. If however, during the course of oxygen inhalation at the 60 or 50 feet depth, nausea, muscular twitching, dizziness, blurring of vision, tremor, irritability, or apprehension supervene, oxygen must be discontinued and treatment completed with the patient breathing air.

During the year 1944, a variety of recompression procedures was used by the U. S. Navy. The most commonly accepted methods are described in Table 1. Although the long oxygen treatment procedure (Table 1) was successfully applied (2) in caring for 49 out of 50 patients suffering from decompression sickness following dives during which helium oxygen mixtures were breathed, the procedure proved to be inadequate for the treatment of decompression sickness following dives during which compressed air was breathed. The recurrence rate was as high as 50 per cent (Table 2).

This difference between the treatment required for decompression sickness resulting from exposure in compressed air and that resulting from exposure in a compressed helium-oxygen atmosphere, can be explained by the more rapid elimination of helium. This occurs because tissues saturated with helium will eliminate this gas as rapidly in an atmosphere of compressed air as in an atmosphere of oxygen since the partial pressure of helium in the alveolar air is maintained throughout decom-

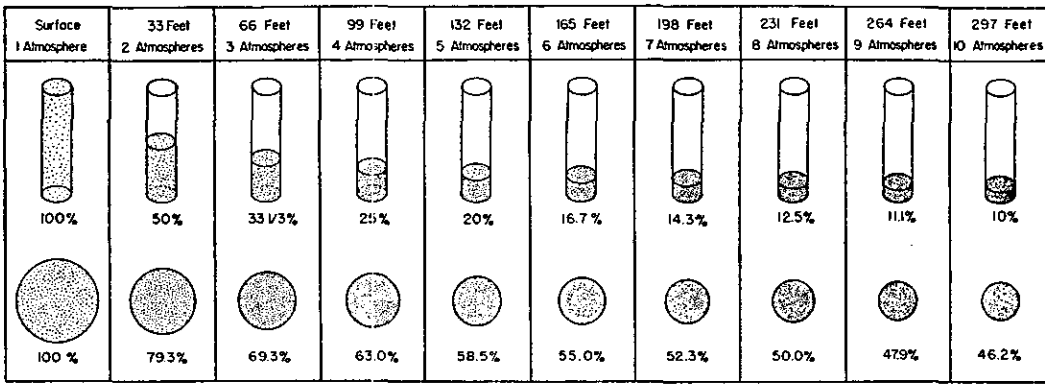

FIG. 1. The top row of figures illustrates the change in gas volume occurring with increasing atmospheric pressure. The bottom row of figures depicts the change in diameter of a gas filled sphere with an elastic wall when the atmospheric pressure is increased. In these calculations the gas was assumed to be dry because the effect of water vapor is negligible at high atmospheric pressures.

pression at a level approaching zero. On the other hand tissues saturated with nitrogen will not eliminate this gas rapidly in an air atmosphere since the partial pressure of nitrogen in the alveolar air remains elevated throughout the entire decompression period.

In verifying the inadequacy of this particular treatment procedure for decompression sickness occurring after dives during which compressed air was breathed, the experimental results of Van Der Aue, et al. (3) confirmed the field experience (Table 2).

water in a pressure diving tank at a pressure equivalent to a depth of 130 feet and then decompressed according to standard navy tables. One-half to one hour following this procedure, the divers were recompressed and then decompressed according to the particular treatment outline under study. The divers seldom developed decompression sickness after the work dive, but there is no doubt that according to calculations based on quantitative data (6), their tissues for several hours afterward contained an amount of nitrogen

TABLE 1

COMMONLY ACCEPTED PROCEDURES FOR THE TREATMENT OF DECOMPRESSION SICKNESS DURING 1944. THE FIGURES REFER TO MINUTES AT EACH DEPTH (STOP)

STOPS (FT.) SEA WATER										
165	140	120	100	80	60	50	40	30	20	10
Short O_2 table*										
			30(air)	12(air)	30(O_2)	30(O_2)	30(O_2)	To surface 5(O_2)		
Short air table*										
			30(air)	12(air)	26(air)	30(air)	35(air)	42(air)	52(air)	68(air)
Long O_2 table**										
30(air)	12(air)	12(air)	12(air)	12(air)	30(O_2)	30(O_2)	30(O_2)	To surface 5(O_2)		
Long air table***										
30(air)	12(air)	12(air)	12(air)	12(air)	26(air)	30(air)	35(air)	42(air)	52(air)	68(air)

* Short O_2 table adopted after reference 4.

** Long O_2 table adopted after references 2, 4, 9, 10.

*** Air tables adopted after references 6, 10.

TABLE 2

RESULTS FOLLOWING THE USE OF VARIOUS TREATMENT PROCEDURES DURING 1944 (TABLE 1)

PROCEDURE USED	CASES TREATED	SUCCESSFUL TREATMENTS	FAILURES (RECURRENCES)	PERCENTAGE FAILURES
Short O_2 table.....	6	6	0	0%
Short air table.....	9	7	2	22%
Long O_2 table.....	10	5	5	50%
Long air table.....	5	3	2	40%
All tables.....	30	21	9	30%

The experimental design for testing a given treatment procedure followed along these lines: Divers were exposed to a one-hour work dive under

in excess of that normally held in solution at atmospheric pressure.

The rationale of subjecting these divers with some excess nitrogen in their tissues to immediate recompression was as follows: The application of a given treatment procedure should under no conditions be followed by decompression sickness. When symptoms occurred following the application of a treatment procedure, it was apparent that this procedure would be inadequate if applied to individuals with symptoms of decompression sickness. It was found that the long treatment procedure employing ninety minutes of oxygen inhalation (Table 1) gave rise to decompression sickness in 6 of 10 divers, 3 of whom required recompression. In order to eliminate the

occurrence of symptoms from this original table, it was necessary to increase the period of oxygen inhalation to one hundred and fifty minutes. In order to make the treatment procedure applicable to all cases of decompression sickness and air embolism, the detailed treatment outline was formulated (Fig. 2).

This treatment procedure was adopted by the Bureau of Medicine and Surgery and the Bureau of Ships and promulgated to the naval service in July, 1945.

DESCEND 25 ft./min. ASCEND 1 min between stops	"BENDS"-PAIN ONLY		SERIOUS SYMPTOMS	
	Pain relieved at depths LESS THAN 66 ft. Use table 1 A if O_2 is not available	Pain relieved at depths GREATER THAN 66 ft. Use table 2 A if O_2 is not available. If pain does not improve within 30 min. at 165 ft. the case is probably not bends. Decompress on Table 2 or 2 A	Serious symptoms include any one of the following. 1. Unconsciousness 2. Convulsions 3. Weakness or inability to use arms and legs. 4. Any visual disturbances. 5. Dizziness 6. Loss of speech or hearing. 7. Severe shortness of breath or "chokes".	
			Symptoms RELIEVED within 30 min. at 165 ft. Use table 3	Symptoms NOT RELIEVED within 30 min. at 165 ft. Use table 4

STOPS		TIME IN MINUTES UNLESS OTHERWISE INDICATED					
Lbs.	Ft.	Table 1	Table 1A	Table 2	Table 2A	Table 3	Table 4
73.4	165			30 (Air)	30 (Air)	30 (Air)	30 to 120 (Air)
62.3	140			12 (Air)	12 (Air)	12 (Air)	30 (Air)
53.4	120			12 (Air)	12 (Air)	12 (Air)	30 (Air)
44.5	100	30 (Air)	30 (Air)	12 (Air)	12 (Air)	12 (Air)	30 (Air)
35.6	80	12 (Air)	12 (Air)	12 (Air)	12 (Air)	12 (Air)	30 (Air)
26.7	60	30 (O_2)	30 (Air)	30 (O_2)	30 (Air)	30 (O_2 or Air)	6 hrs. (Air)
22.3	50	30 (O_2)	30 (Air)	30 (O_2)	30 (Air)	30 (O_2 or Air)	6 hrs. (Air)
17.8	40	30 (O_2)	30 (Air)	30 (O_2)	30 (Air)	30 (O_2 or Air)	6 hrs. (Air)
13.4	30	↑	60 (Air)	60 (O_2)	2 hrs. (air)	12 hrs. (air)	First 11 hrs. AIR Then 1 hr O_2 or AIR
8.9	20	5 (O_2)	60 (Air)	↑	2 hrs (air)	2 hrs. (air)	First 1 hr. AIR Then 1 hr. O_2 or AIR
4.5	10	↓	2 hrs (air)	5 (O_2)	4 hrs. (air)	2 hrs. (air)	First 1 hr. AIR Then 1 hr. O_2 or AIR
SURFACE		↓	1 min (air)	↓	1 min (air)	1 min (air)	1 min (O_2)

If symptoms return DURING treatment recompress to depth of relief but never less than a depth of 30 ft. and complete decompression from this depth according to table 4.

If dizziness, nausea, muscular twitching or blurring of vision occurs while breathing oxygen, remove mask and proceed as follows: (a) if using table 1, complete remaining stops of table 1A; (b) if using table 2, complete remaining stops of 2A; (c) if using table 3, complete remaining stops of table 3 breathing air. At the discretion of the Medical Officer, oxygen breathing may be resumed at the 40 and 30 foot stops for a total of 90 minutes if using table 1 or 3 and 150 minutes if using table 2.

FIG. 2. Treatment of caisson disease and air embolism.

ANALYSIS OF CASES

To date 113 reports of decompression sickness treated in accordance with these procedures (Fig. 2) have been analyzed. The patients presented the usual symptoms of decompression sickness

with localized pain being the most common (Table 3). Twenty-nine patients presented symptoms referable to the central nervous system. One patient developed the severe type of asphyxia known as "the chokes". In the 107 cases which exhibited localized pain (bends), the upper extremity was involved seventy-one times and the lower extremity twenty-eight times. The upper and lower extremities both were involved six times. The pain was localized in the trunk muscles twice. The elbow and shoulder joints were the sites most frequently involved in the upper extremity and the knee joint was involved most frequently in the lower extremity.

Of the 113 patients in this series, 17 had symptoms following "saturation dives". A "saturation dive" is an experimental procedure in which a subject at rest is exposed in a recompression chamber for periods of twelve hours or longer. Following the saturation exposures the lower extremity was involved five times more frequently than the upper extremity.

Symptoms were relieved in 36 patients (about 32 per cent) when they were recompressed to pressures less than that equivalent to a diving depth of 33 feet (Table 4). Twenty-eight (about 25 per cent) were relieved at depths between 34 and 66 feet and 20 (about 15.5 per cent) were relieved between 67 and 164 feet. Twenty-nine (about 25.5 per cent) of the patients were not relieved of their symptoms until a pressure equivalent to a diving depth of 165 feet was reached. Twenty of these patients were relieved immediately at the 165-foot depth but 9 patients required periods varying from five to seventy-two minutes before relief was obtained. The pressure required to obtain relief appears to be related directly to the time interval between the onset of symptoms and the start of the treatment.

The time elapsing between completion of the dive and onset of symptoms varies widely in decompression sickness (Table 5). In 14 of the 113 patients, symptoms occurred during or immediately after decompression. In 84.7 per cent of

TABLE 3

SYMPTOMS OF DECOMPRESSION SICKNESS IN 113 DIVERS TREATED IN ACCORDANCE WITH THE MODIFIED PROCEDURES

SYMPTOMS	NUMBER OF PATIENTS TREATED IN ACCORDANCE WITH EACH TABLE						TOTAL NUMBER OF PATIENTS WITH EACH SYMPTOM
	1	1A	2	2A	3	4	
Localized pain	50	7	25	12	13	0	107
Numbness	2	1	1	3	2	1	10
Muscular weakness	3	0	1	2	3	1	10
Rash	4	0	4	1	0	0	9
Visual disturbances	0	0	0	1	7	0	8
Vertigo	0	0	0	1	3	0	4
Aphasia	0	1	0	0	1	0	2
Headache	0	0	1	0	1	0	2
Unconsciousness	0	0	0	1	1	0	2
Nausea	0	0	0	1	0	0	1
Chokes	0	0	0	0	1	0	1
Number of patients exhibiting a single symptom	41	7	18	6	7	0	79
Number of patients exhibiting two of the above symptoms	9	1	7	5	6	1	29
Number of patients exhibiting more than two of the above symptoms	0	0	0	1	4	0	5
Number of patients in which pain was the only symptom	41	7	18	6	5	0	77
Number of patients in which localized pain was *not* a symptom	0	1	0	0	4	1	6

TABLE 4

DEPTH TO WHICH 113 PATIENTS WITH DECOMPRESSION SICKNESS WERE COMPRESSED BEFORE RELIEF OF SYMPTOMS WAS OBTAINED. ONE FOOT IS EQUIVALENT TO A PRESSURE OF 0.445 POUNDS PER SQUARE INCH GAGE

DEPTH OF RELIEF (FEET)	NUMBER OF PATIENTS RELIEVED AT EACH DEPTH	
1 to 33	36	31.8%
34 to 66	28	24.8%
67 to 99	13	11.5%
100 to 132	6	5.3%
133 to 164	1	0.9%
165	29	25.7%

TABLE 5

TIME OF ONSET OF SYMPTOMS AFTER EXPOSURE TO PRESSURE

TIME OF ONSET	NUMBER OF CASES
During or immediately after decompression	14
Within ½ hour	15
½ to 1 hour	12
1 to 2 hours	16
2 to 4 hours	20
4 to 6 hours	18
6 to 8 hours	4
8 to 10 hours	4
10 to 12 hours	4
12 to 14 hours	1
14 to 16 hours	0
16 to 18 hours	2
18 to 24 hours	2

TABLE 6

RESULTS OF TREATMENT IN 113 PATIENTS WITH DECOMPRESSION SICKNESS USING THE MODIFIED TREATMENT PROCEDURES

TABLE NUMBER	TOTAL NUMBER OF PATIENTS TREATED	RESULT OF TREATMENT		
		Recovered	Recurred	Residual
1	50	47	3	0
1A	8	8	0	0
2	25	24	1	0
2A	12	12	0	1
3(O_2)	7	7	0	0
3(Air)	10	10	0	0
4	1	1	0	1

the patients the disease made its presence known within six hours after the dive. The onset of symptoms was delayed as long as twenty-four hours in one case. Delayed symptoms occur more frequently following saturation dives.

Of the 113 divers treated according to the modified treatment procedures, 4 suffered a recurrence of symptoms and required subsequent recompression (Table 6). One additional diver who neglected to report the paresthesia and weakness in his hand until twenty-one and one-half hours after onset, had a residual anesthesia of the palm following treatment (Treatment Table 4, Fig. 2). Of the 4 recurrences, 3 occurred following the employment of Treatment Table 1 and 1 following Treatment Table 2 (Fig. 2). Two of the recurrences following the employment of Treatment Table 1 can be attributed to insufficient recompression. These patients' symptoms were relieved at 70 and 78 feet respectively, yet they were only recompressed to 100 feet instead of to 165 feet as recommended (Fig. 2). The other treatment failure following the employment of Treatment Table 1 cannot be explained. The recurrence following the procedure in Treatment Table 2 (Fig. 2) can be attributed to a faulty oxygen breathing apparatus which permitted a significant dilution of the oxygen with air.

Four of the 75 patients treated in accordance with the two oxygen tables (Treatment Tables 1 and 2, Fig. 2) developed symptoms of oxygen poisoning. A resumé of their histories is presented below:

Case 1.—The patient developed symptoms of decompression sickness sixteen hours after the dive. Recompression to 100 feet was started shortly after the onset of symptoms. Decompression in accordance with Treatment Table 1 (Fig. 2) was started. After breathing oxygen at an equivalent depth of 60 feet for thirty minutes, the patient became nauseated. The nausea was followed by rapid twitching of the facial muscles, and a generalized epileptiform convulsion. The convulsion lasted three to five minutes. Oxygen breathing was discontinued and toxic symptoms were relieved. This man had consumed a considerable amount of alcohol during the period between the completion of his dive and his subsequent recompression. Also, he had shown a low tolerance for oxygen under pressure on previous occasions.

Case 2.—The patient developed symptoms of decompression sickness twenty-five minutes after the dive. The symptoms gradually subsided but then reappeared four and one-half hours after the dive. Recompression to 100 feet was started

shortly after the reappearance of the symptoms. During subsequent decompression from 100 feet in accordance with Treatment Table 1 (Fig. 2), the patient became nauseated after breathing oxygen eighteen minutes at an equivalent depth of 60 feet. The toxic symptom was relieved when oxygen administration was discontinued.

Case 3.—The patient developed symptoms of decompression sickness nine hours after his dive. Recompression to 165 feet was started three and one-half hours after the onset of symptoms. During decompression from 165 feet in accordance with Treatment Table 2 (Fig. 2), the patient became nauseated after breathing oxygen for twenty-six minutes at an equivalent depth of 60 feet. The toxic symptom was relieved when oxygen administration was discontinued.

Case 4.—The patient developed symptoms of decompression sickness within five minutes after his dive. Recompression to 165 feet was started shortly after the onset of symptoms. During decompression from 165 feet in accordance with Treatment Table 2 (Fig. 2), the patient breathed oxygen for thirty minutes at 60 feet, thirty minutes at 50 feet, and twenty-one minutes at 40 feet. After breathing oxygen for twenty-one minutes at 40 feet, the patient became disoriented and paranoic. The toxic symptoms were promptly relieved when oxygen administration was discontinued.

It is interesting to compare the results obtained when using these modified treatment procedures with those obtained when using other methods of recompression. During the year 1945, 82 cases of caisson disease were reported. Of these, 65 cases were treated with the new procedures and 17 patients were treated with various other procedures. Three of the patients (4.6 per cent) treated with the new procedures developed recurrence of symptoms. Six of the 17 patients treated with the other procedures developed recurrences, a recurrence rate of over 35 per cent.

Although the number of patients treated with the new treatment procedures is too small to draw definite conclusions, it is apparent that these procedures show promise of being the best devised to date. One portion of the new procedures, Treatment Table 4 (Fig. 2), has been used in only one case and no conclusion regarding its value can be drawn.

Summary

1. A comprehensive tabular outline for the treatment of decompression sickness has been developed by workers at the Experimental Diving Unit and the Naval Medical Research Institute which includes three basic principles, (a) the limitation of the maximal pressure applied during recompression to 65 pounds per square inch gage and the maintenance of this pressure for periods of at least thirty minutes and for as long as two hours, (b) a prolonged recompression for periods of twelve to twenty-four hours or longer at pressure levels equivalent to depths between 30–60 feet, and (c) the inhalation of oxygen at pressure levels equivalent to 60 feet or less in order to promote the more rapid elimination of nitrogen.

2. This treatment outline has served as a guide in the treatment of 113 divers who developed decompression sickness and in 109 of the patients the treatment was successful. The other 4 patients developed recurrences of their symptoms following treatment. Of the 4 recurrences, 2 may be attributed to insufficient recompression and 1 was due to the employment of faulty oxygen breathing apparatus.

3. Four of 75 patients treated with the procedures involving the use of oxygen developed symptoms of oxygen toxicity, 3 of them mild and 1 terminating with a convulsion. These symptoms are relieved promptly by discontinuing the administration of oxygen.

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Rheologic Impairment of the Microcirculation During Decompression Sickness[1]

C. H. WELLS, T. P. BOND, M. M. GUEST, AND C. C. BARNHART

Department of Physiology, University of Texas Medical Branch, and Marine Biomedical Institute jointly sponsored by the University of Texas Medical Branch and Texas A & M University, Galveston, Texas 77550

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Eighteen dogs exposed for 1 hr to 5% O_2, 95% N_2 at a pressure equivalent to 200 ft of seawater were decompressed to sea level pressure within 10 min. One hour after decompression a severe impairment of mesenteric microcirculation with pronounced erythrocyte aggregation was evident. Small bubbles frequently appeared but passed through the microcirculatory channels without apparent difficulty. Bubble emboli were not observed. The blood viscosity 1 hr after decompression, compared with the precompression viscosity, increased by 24% at a shear rate of 230 sec^{-1} and by 63% at 5.75 sec^{-1}. Changes in viscosity were accompanied by significant increases in hematocrit and in partial thromboplastin times. Euglobulin lysis times were significantly shortened 1 hr postdecompression. Partial thromboplastin times of normal dogs not subjected to compression and decompression became significantly prolonged after their plasma had been foamed by shaking in air. Information provided by this study and related evidence from other laboratories indicate that bubble embolism is not a significant factor in production of the microcirculatory aberrations of decompression sickness. However, introduction of large gas–liquid interfaces could be responsible for altering the components and rheologic characteristics of the blood.

INTRODUCTION

Although many of the manifestations of decompression sickness have been ascribed to bubble embolism, a growing body of evidence suggests that the pathogenesis of decompression sickness is more complex. Direct observation of microcirculatory flow during or shortly after decompression has been reported by several investigators. A pattern of reduced capillary flow, scattered stasis in microcirculatory channels, increased aggregation of erythrocytes, and increased flow through arteriovenous shunts has been described (End, 1938; Wagner, 1945; Buckles, 1968; Heimbecker *et al.*, 1968). Hemoconcentration and reduction in plasma volume have also been observed (Cockett and Nakamura, 1964; Cockett *et al.*, 1965; Brunner *et al.*, 1964; Barnard *et al.*, 1966). These changes may occur without evidence of bubble embolism (Wagner, 1945; Heimbecker *et al.*, 1968). An apparently similar reduction in microcirculatory flow with an associated erythrocyte aggregation is characteristically seen in animals

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subjected to any of a variety of physically traumatic events (Knisely *et al.*, 1945; Knisely *et al.*, 1947; Bigelow *et al.*, 1949). Although controversy persists about the nature of the processes responsible for these microcirculatory aberrations, an elevation in blood viscosity has been reported as a correlate of the changes in blood flow (Bergentz *et al.*, 1963; Hoyt *et al.*, 1964; Parker, 1968; Schoen *et al.*, 1971).

This study was designed to investigate possible changes in blood viscosity following decompression and to monitor hematocrit, erythrocytic aggregation, and some plasma components of the blood coagulation and fibrinolytic systems.

METHODS

Eighteen adult mongrel dogs, anesthetized with pentobarbital, were subjected to a mixture of 5% O_2 and 95% N_2 at a pressure equivalent to 200 ft of seawater for 60 min. The animals were then decompressed to 1 atm pressure at a rate of 20 ft/min.

The mesentery of each animal to be compressed was exposed by a midline abdominal incision, and the microcirculation within that tissue was recorded before and after compression-decompression by cinephotomicrography at magnifications from ×10 to ×90 and exposure rates from 24 to 300 frames per second (Bond and Guest, 1971). Single frame 35-mm photographs of the mesenteric microcirculation were also made.

Blood samples were collected from a catheter in a carotid artery before compression, immediately after decompression, and 60 min after decompression. Viscosity of heparinized blood was measured at each of six shear rates ranging from 230 to 5.75 sec^{-1} using a Wells-Brookfield LVT plate-cone viscometer. Coagulation time was estimated by the method of Lee and White (1913); fibrinogen concentration by the method of Ware, Guest, and Seegers (1947); prothrombin time by Quick's one-stage assay (1957); and partial thromboplastin time (PTT) by the method of Rodman *et al.* (1958) except that soybean phosphatide was substituted for cephalin used in the original test (Bond *et al.*, 1962). Reciprocals of the euglobulin lysis times measured by the technique of Celander and Guest (1964) were multiplied by 100 to convert times to units.

Data derived from samples collected immediately after decompression were compared with corresponding values from the same animal's precompression samples, using Student's *t* test for paired data. Data from samples collected 1 hr after decompression were similarly compared with corresponding precompression values. Ten of the 18 animals used in this study lived through the decompression period but failed to survive for 1 hr following decompression. Thus, there were 18 sets of data available for analyses from samples collected immediately after decompression but only 8 sets of data from samples collected 1 hr after decompression.

To determine the effect of a large gas-liquid interface citrated blood was obtained from dogs which had not been compressed. The plasma was separated by centrifugation. Base line assays for coagulation and fibrinolysis were performed as on blood from animals subjected to compression and decompression. The remaining plasma was then foamed by shaking for 5 min in contact with air. The continuous liquid phase was separated from the foam. Assays were performed on both the continuous liquid phase and on the foam phase after the foam had reverted to a continuous liquid, free of air bubbles.

RESULTS

Cinephotomicrography of the mesenteric microcirculation immediately after decompression revealed little change in microcirculatory flow and minimal formation of erythrocyte aggregates. Bubbles of approximately 10 μ diameter frequently appeared but passed readily through the microvasculature. No bubble embolism was seen. The films taken 30-60 min after decompression showed severe impairment of microcirculatory flow with scattered stasis and widespread formation of erythrocyte aggregates.

FIG. 1. Mesenteric microcirculation 1 hr after decompression.

Bubbles of approximately 10 μ diameter were again evident in the cinephotomicrographs of the microcirculation but passed through the microvessels without apparent difficulty. No evidence of bubble embolism was seen. Figure 1 is a microphotograph taken 1 hr after decompression, illustrating aggregation of erythrocytes. At this magnification the 10 μ bubbles are not usually discernible.

Analyses of blood viscosity are summarized in Fig. 2. The viscosities of blood samples collected immediately after decompression were slightly greater than corresponding precompression (base line) values at each of the six shear rates tested (5.75–230 sec^{-1}). These values differed significantly ($p > .05$) at two of the six shear rates tested. A more pronounced, shear rate-dependent rise in blood viscosity was found in samples collected 1 hr after decompression. The mean viscosities increased progressively from 124% of control values at a shear rate of 230 sec^{-1} to 163% of control at a shear rate of 5.75

sec^{-1}. These values were significantly greater ($p > .05$) than corresponding control values at each of the six shear rates studied.

The mean hematocrit of samples collected prior to compression was 34, immediately following decompression 35 and 1 hr after decompression 42. The difference between the latter value and its corresponding base line value (precompression value) was significant ($p > .05$).

No significant changes from base line values were found in plasma fibrinogen concentrations, Lee–White coagulation times, or one-stage prothrombin times either immediately after decompression or in samples collected 1 hr after decompression.

PTT in samples collected immediately after decompression were slightly but not significantly greater than in samples collected from the same animals prior to compression. The PTT of samples collected 1 hr after decompression was 114% of that of precompression samples. This difference is significant ($p > .05$). In the liquid fraction of foamed canine plasma the mean PTT was 20% longer than in unfoamed aliquots of the same plasma. This difference is significant ($p > .05$). Foaming plasma failed to cause significant changes in any other of the performed coagulation or fibrinolytic assays.

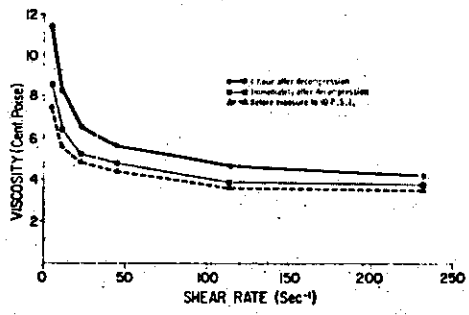

FIG. 2. Mean blood viscosity of dogs subjected to decompression.

Euglobulin lysis times (ELT) were less in samples collected 1 hr after decompression than in precompression samples. Converted to units, the precompression activity was 0.82 units immediately after decompression, and the 1 hr postdecompression activity was 1.72 units. This difference is significant ($p > .05$). Euglobulin lysis units in blood samples collected immediately after decompression (0.85) are not significantly different from the precompression values.

DISCUSSION

From analyses of our cinephotomicrographic records, reduced velocity in larger vessels and stasis in many venules and capillaries occurred within an hour after decompression. Bubble embolism was never observed although bubbles, which passed easily through the capillaries, did repeatedly appear (Bond *et al.*, 1970). Swindle (1937), Wagner (1945), and Heimbecker *et al.* (1968) have also described impairment in microcirculatory flow during decompression sickness in the absence of demonstrable bubble microembolism.

It has been suggested that the alterations in flow during decompression sickness result from aggregates of erythrocytes which tend to block microcirculatory channels. Similar reductions in microcirculatory flow and intravascular aggregation of erythrocytes have been reported in a variety of other traumatic events including crush (Knisely *et al.*, 1945; Bigelow *et al.*, 1949), thermal injury (Heimbecker and Bigelow, 1950; Guest and Bond, 1968; Schoen *et al.*, 1970), tissue ischemia (Chambers *et al.*, 1944; Bigelow *et al.*, 1949), and infections (Knisely *et al.*, 1947; Knisely *et al.*, 1964). Our

TABLE 1

BLOOD COAGULATION STUDIES IN DOGS FOLLOWING DECOMPRESSION[a]

	Precompression all animals	Immediately after decompression, all animals	Precompression animals surviving 1 hr after decompression	One hour after decompression
Plasma fibrinogen concentration (mg %)	329±14	318±18	324±25	306±33
Lee–White coagulation time (min)	5.8±0.3	6.0±0.8	5.9±0.5	4.8±0.4
Prothrombin one-stage time (sec)	11.4±0.3	11.7±0.3	11.7±0.4	11.9±0.4
Partial thromboplastin time (sec)	36.6±2.1	39.2±2.6	34.7±2.5	42.5±5.3
Hematocrit	34.3±1.4	34.9±1.3	33.6±1.0	42.1±3.0
Euglobulin units	82±7[b]	85±8	97±11[b]	172±30

[a] Values presented are means and standard errors of means.

[b] The mean fibrinolytic activity of samples collected before compression from those animals that subsequently survived less than 1 hr following decompression was 69 ± 8 euglobulin units.

photographic recordings of microcirculatory events during decompression sickness confirmed that aggregation of erythrocytes occurs (Fig. 1) and is especially marked 1 hr following decompression.

Viscosities of blood samples collected 1 hr after decompression were substantially greater than corresponding precompression values. The magnitude of the changes varied with shear rate, ranging from an increase of 24% at a shear rate of 230 sec^{-1} to 63% at 5.75 sec^{-1}. Although the effects of an increase in viscosity of this magnitude on flow in the microcirculation are difficult to quantitate, it would appear that the resultant increase in resistance to flow could be a major cause of the circulatory impairment in decompression sickness.

A number of factors have been shown to augment the viscosity of blood. The most important of these are an increase in hematocrit (Merrill *et al.*, 1963c; Gregersen *et al.*, 1965; Putnam *et al.*, 1965), erythrocyte aggregation (Merrill *et al.*, 1963a; Chien *et al.*, 1967b; Schmidt-Schoenbein *et al.*, 1967), and a decrease in erythrocyte flexibility (Schmidt-Schoenbein *et al.*, 1969; Chien *et al.*, 1967a; Seaman and Swank, 1967). Indirectly, through its effect on erythrocyte aggregation, an increase in the fibrinogen concentration also augments the viscosity of blood (Merrill *et al.*, 1963b; Merrill *et al.*,

1966; Chien *et al.*, 1966). In our decompressed animals no change in fibrinogen concentration was observed and we have no reason to suspect a change in red cell flexibility. On the other hand, the hematocrit increased and erythrocyte aggregation was observed in the microcirculatory photographic records. These factors appear to be responsible for the increase in blood viscosity and *pari passu* for an increase in resistance to flow in the microcirculatory bed.

The basic mechanisms underlying the increase in hematocrit and erythrocyte aggregation in decompression sickness are currently uncertain. A reasonable explanation for the rise in hematocrit is that plasma is lost because of an increase in capillary

TABLE 2

BLOOD COAGULATION STUDIES OF FOAMED DOG PLASMA[a]

	Plasma before foaming	Foamed plasma	
		Foamed fraction	Fluid fraction
Plasma fibrinogen concentration (mg %)	394±25	399±25	395±25
Prothrombin one-stage time (sec)	11.2±0.5	11.4±0.5	11.1±0.5
Partial thromboplastin times (sec)	46.2±2.9	47.5±3.0	55.4±3.8
Euglobulin units	66.2±4.0	68.0±4.0	61.0±3.6

[a] Values above are means and standard errors of means.

permeability. More obscure is the reason for the aggregation of erythrocytes in the absence of an increase in fibrinogen concentration. Heimbecker *et al.* (1968) explored the possibility that hypercoagulability, presumably through enhancement of erythrocyte aggregation, is responsible for low capillary perfusion in decompression sickness. However, these investigators failed to demonstrate a change in blood coagulation by measuring polystyrene clotting times. On the other hand, Aggazzotti (1933) has reported a shortened coagulation time in a majority of dogs and rabbits decompressed from 6 to 11 atm, and Barthelemy (1963) has reported reduction in the severity of decompression sickness in rabbits and men treated with heparin. In our study, the only significant change in coagulation assays was the prolongation of PTT in blood samples collected 1 hour after decompression (Table 1).

A significant prolongation of the PTT occurred in the decompressed animals when intravascular bubbles were present and in plasma foamed *in vitro*. Thus, the possibility exists that the alteration in activity of an intrinsic procoagulant factor or factors is related in some manner to the abnormal presence of gas–liquid interfaces. Prolongation of the PTT might be interpreted as an indication that conversion of prothrombin to thrombin occurred in the decompressed dogs. A prolongation of the PTT, due to a decrease in the activity of factor VIII, has been reported by Penick *et al.* (1958) during experimental intravascular coagulation in dogs.

A highly significant increase in euglobulin lysis units was observed when the activity 1 hr after decompression was compared with the precompression level. The increase in fibrinolytic activator apparently was not due to interaction at a gas liquid interface

per se since no increase in activity was observed in the liquid or foam fraction of foamed plasma. The euglobulin assay is a measure of plasma activator of the fibrinolytic system and the activator appears to be derived from the endothelium of blood vessels (Guest, 1966). An increase in plasma activator occurs with vasodilation or the opening of previously stagnant segments of the circulation (Holemans and Silver, 1969).

A surprising observation was that in animals surviving for 1 hr postdecompression, the precompression euglobulin lysis units were significantly greater than in non-surviving animals. If the disability resulting from decompression is in part due to a hypercoagulable state, more effective fibrinolytic activation might give some protection against the lethal effects of decompression.

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Treatment of Bends with Oxygen at High Pressure

ROBERT D. WORKMAN, M. D.

DECOMPRESSION SICKNESS occurs as a result of the formation of intra- and extra-vascular gas bubbles following inadequate decompression from pressure exposure. While most commonly seen in divers and caisson workers, it also occurs during exposure to less than atmospheric pressure. The magnitude of the disability resulting relates to both the site of lodgment of the bubbles, their number and size. Therapy of this condition is directed toward the reduction in size and ultimate resolution of the bubbles.

Pol and Watelle[5] in 1854 recognized the causative factors of decompression sickness in caisson workers and established recompression as the primary method of treatment to afford relief of symptoms. In 1897, Zuntz[13] initiated the use of oxygen breathing in conjunction with recompression to hasten bubble resolution by increasing the outward gradient for nitrogen. However, due to the known toxicity of oxygen when breathed at high pressure, its use was not widely accepted. Von Schrotter[9], in 1906, again suggested the use of oxygen breathing to hasten nitrogen elimination in treatment of decompression sickness.

Behnke and Shaw[1] in 1937 established some of the basic principles underlying recompression as a therapeutic procedure for decompression sickness, and outlined a method utilizing oxygen breathing. The purpose of recompression was to provide prompt and lasting relief of the signs and symptoms of decompression sickness and air embolism. To accomplish this purpose, any recompression procedure must be designed with three specific objectives in mind: (1) to reduce the bubbles to asymptomatic size in a short time, (2) to ensure that these bubbles do not again become symptomatic during subsequent ascent, and (3) to conduct the decompression phase in such a way that new bubbles do not form.

Using a combination of recompression and oxygen breathing, Yarbrough and Behnke[12] reported the successful treatment of 49 of a total of 50 divers with decompression sickness which occurred after exposure to helium-oxygen atmospheres at high pressure. However, through the years opinion has varied as to the optimum procedure for exposure to pressure and subsequent decompression to be used. In general, the recompression treatment of decompression sickness has been related to the depth of the dive, or to the pressure required for relief of symptoms. The U. S.

The opinions or assertions contained herein are those of the author and are not to be construed as reflecting the views of the Navy Department or the Naval Service at large.

The address of Capt. R. D. Workman, MC, USN, is Naval Medical Research Institute, Bethesda, Maryland.

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Navy Treatment Tables[1] are based on use of a pressure greater than that required to relieve symptoms, without regard for the depth of the dive inducing symptoms. The patient is recompressed, breathing air, to 4 or 6 atmospheres absolute pressure (ATA) for a period of ½ to 2 hours, followed by slow decompression to one ATA to prevent reformation of bubbles in the already compromised circulation of injured tissues. In these tables, which have been in use without modification for over 20 years, the duration of treatment varies from 2.5 to 38 hours, depending on the seriousness of the initial injury and the response of the patient to recompression therapy.

The use of oxygen breathing at increased pressure has had a prominent place in the standard U. S. Navy Treatment Tables, aimed specifically at objectives 2 and 3 stated previously. Since the process of gas diffusion from bubbles and tissues may be slow, administration of oxygen at increased pressure is desirable to accelerate the process. Practical application of pure oxygen breathing is limited by toxicity to a pressure of 3 ATA. In U. S. Navy Treatment Tables 1, 2 and 3, oxygen is breathed during return to atmospheric pressure at 60, 50, 40 and 30 feet, whereas in Table 4 oxygen breathing again on decompression. is limited to depths of 30, 20 and 10 feet, to aid in the final decompression to one ATA.

The U. S. Navy Treatment Tables were adopted for use on a worldwide basis and achieved significant success after their standardization. This success was chiefly in the treatment of naval divers, and was based on opportunity for early diagnosis of injury and prompt recompression in chambers located at the site of diving operations. With the increase in civilian recreational diving made possible by the development of self-contained underwater breathing apparatus (SCUBA), at sites distant from recompression chambers, naval facilities throughout the world began to receive patients for treatment who had developed bends as a result of grossly inadequate decompression. The severity of injury was also accentuated by delay in reporting for treatment until disability was extensive, serious or fixed. Especially in those cases which had been delayed in treatment, the injury often persisted following recompression possibly due to effects of ischemia, edema and thrombosis.

For example, during the years 1963 and 1964, the U. S. Navy Experimental Diving Unit received reports of 133 cases of decompression sickness in which the standard U. S. Navy Treatment Tables were applied. In 32 instances (24%) the initial recompression treatment did not result in full relief of symptoms, or there was a re-appearance of symptoms on decompression. Treatment Tables 3 and 4 accounted for 62 of the therapeutic exposures and 29 of the failures, a 47% incidence of failure of the first treatment. There were no instances of failure with Table 3 and 4, however, when pressure exposure of Navy divers was conducted in accordance with procedures promulgated in the U. S. Navy Diving Manual.[1]

Of great concern to medical personnel responsible for treatment of these severe injuries, has been death of patients occurring either at maximum treatment depth, or following recurrence and exacerbation of signs and symptoms during the subsequent decompression phase. The difficulty encountered in eliminating inert gas from injured tissues in the face of circulatory impairment was evident, and consideration was given to avoiding inert gas uptake in tissues during the compression treatment by use of oxygen breathing at pressures where this could be carried out without risk of oxygen toxicity. Another important advantage to be gained is the increase in oxygenation of injured, ischemic tissues distal to the embolic obstruction.

OXYGEN TREATMENT AT INCREASED PRESSURE

Several cases of decompression sickness were treated at the U. S. Navy Experimental Diving Unit with a method which includes recompression to 60 feet (2.8 ATA) with oxygen breathing for a period of time sufficient to effect bubble resolution, followed by slow decompression to one ATA, with oxygen breathing continued throughout. Initial results of this procedure in treatment of both pain and serious symptoms were so promising that more extensive evaluation of the method was conducted at the Experimental Diving Unit in Washington, the Submarine Medical Center in New London and the Submarine Base at Pearl Harbor.

The objective of the oxygen method is to expose bubbles to the optimum pressure gradient for rapid resolution, while still permitting maximum safe oxygenation of tissues with circulation impaired by bubble emboli. In this manner, cellular function can be maintained in ischemic vital areas by interrupting the invidious cycle of ischemia, hypoxia, edema, obstruction of circulation in adjacent tissues and further ischemia. Additional inert gas saturation of tissues is also limited during recompression while the patient breathes oxygen to greatly diminish the risk of initiating bubble formation in tissues during subsequent decompression.

First experience in use of the minimal recompression oxygen breathing method in 79 cases of decompression sickness and air embolism was reported in 1965 by Goodman and Workman.[4] Additional experience in treatment of a total of 123 cases of decompression sickness employing this method was reported in 1967 by Bornmann.[2] The results of treatment reported were an 85% initial, and a 94% overall success rate. On 22 August 1967, the Chief, Bureau of Medicine and Surgery, Department of the Navy, approved the use of this method in BUMED INSTRUCTION 6420.2. Treatment Tables 5, 5A, 6 and 6A with instructions for their use were promulgated in this instruction. The development of this procedure and experience with its use to date is detailed in this report.

PROCEDURE FOR USE OF OXYGEN

A provisional treatment format of recompression with oxygen breathing by patients was developed, with

an indication for abandonment of the treatment system in favor of standard air breathing recompression procedures in the event that relief of symptoms and signs did not occur (Figure 2). The format was as follows:

(1) Recompression to 33 feet (2 ATA) breathing oxygen. If relief of all symptoms was complete within 10 minutes, this depth was maintained for an additional 30 minutes.

(2) Decompression by continuous ascent at the rate of one foot per minute.

(3) If relief was not complete at 33 feet, the patient was further compressed to 60 feet (2.8 ATA) where similar provisions were stipulated for relief time and treatment time.

(4) Decompression by continuous ascent at the uniform rate of one foot per minute, therefore, requiring 60 minutes to return to one ATA.

(5) Incomplete relief at 60 feet was to be followed by recompression to 165 feet (6 ATA) with subsequent treatment on a U. S. Navy Treatment Table. The need for this procedure was never encountered.

On the basis of the results with the early cases treated, *initial recompression directly to 60 feet* (2.8 ATA) was established as a requirement of the method. The 33 feet (2 ATA) trial of relief was eliminated. Retrospective statistical study showed that the total oxygen breathing time and the full treatment depth were significantly related to treatment adequacy. The *minimal requirements for adequacy were determined to* be 60 feet treatment depth, 30 minutes oxygen breathing at this depth, and 90 minutes total treatment time with oxygen breathing. Alternation of oxygen breathing with air for periods of 5 to 15 minutes was introduced to reduce risk of oxygen toxicity to a minimum. Two final treatment schedules were then developed on this basis, with time for relief of symptoms exceeding 10 minutes determining the use of the longer schedule format. Subsequently, the longer schedule of 285 minutes duration (Table 6 of Figure 1) has been used as a conservative measure in treatment of patients with symptoms other than pain, though many treatments of cases with serious symptoms were successful with use of the shorter 135 minute schedule

FIGURE 1

METHOD USED WHEN RELIEF OF PAIN IS COMPLETE WITHIN 10 MINUTES AT 60 FEET

TABLE 5

DEPTH (FEET)	TIME (MINUTES)	BREATHING MEDIA	TOTAL ELAPSED TIME (MINUTES)
60	20	O_2	20
60	5	AIR	25
60	20	O_2	45
60-30	30	O_2	75
30	5	AIR	80
30	20	O_2	100
30	5	AIR	105
30-0	30	O_2	135

OXYGEN TIME Commence O_2 breathing prior to descent. Descent time is not counted as time at 60 feet.

COMPRESSION Normal rate of descent is 25 feet per minute. If serious symptoms are present descend as rapidly as possible. If symptoms are of pain only do not exceed a rate tolerable to the patient.

DECOMPRESSION Ascent is continuous at 1 foot per minute. Do not compensate for slowing of the rate by subsequent acceleration. Do compensate if the rate is exceeded. If necessary, halt ascent and hold depth *while ventilating* the chamber.

INSIDE TENDER Tender routinely breathes chamber air. If the treatment schedule is lengthened or if the treatment constitutes a repetitive dive for the tender, he must *breathe oxygen for the final* 30 minutes of ascent from 30 feet to the surface.

SERIOUS SYMPTOMS Unconsciousness, convulsions, weakness or inability to use arms or legs, air embolism, any visual disturbances, dizziness, *loss of speech or hearing*, chokes, bends under pressure.

METHOD USED WHEN RELIEF OF PAIN IS NOT COMPLETE WITHIN 10 MINUTES AT 60 FEET OR SERIOUS SYMPTOMS ARE PRESENT

TABLE 6

DEPTH (FEET)	TIME (MINUTES)	BREATHING MEDIA	TOTAL ELAPSED TIME (MINUTES)
60	20	O_2	20
60	5	AIR	25
60	20	O_2	45
60	5	AIR	50
60	20	O_2	70
60	5	AIR	75
60-30	30	O_2	105
30	15	AIR	120
30	60	O_2	180
30	15	AIR	195
30	60	O_2	255
30-0	30	O_2	285

CHOICE OF TABLE If completeness of relief is doubtful after 10 minutes of oxygen breathing at 60 feet use Table 6.

RECURRENCE If symptoms recur or if new symptoms appear, return to 60 feet and re-treat the patient on Table 6.

LENGTHENED TREATMENT Table 6 can be lengthened by an additional 25 minutes at 60 feet (20 minutes O_2 - 5 minutes air) or an additional 75 minutes at 30 feet (15 minutes air - 60 minutes O_2) or both.

RELIEF NOT COMPLETE If relief is not complete at 60 feet, proceed with Table 6 and observe patient's condition closely for any change, lengthen the schedule if thought necessary, or compress to 165 feet and treat patient on Table 2, 2A, 3 or 4 as appropriate.

Fig. 1. Treatment format of Table 5 and Table 6 with directions *for application.*

when relief of symptoms occurred within 10 minutes at 60 feet. The final treatment format, designated Tables 5 and 6, appears in Figure 1. Guidance in administration of oxygen is provided in Figure 2.

A modification of U. S. Navy Treatment Tables 5 and 6 has been developed by medical officers at the Submarine Medical Center, Submarine Base, New London, Connecticut for specific application to treatment of traumatic air embolism occurring in personnel during training for buoyant ascent from submarines. This modification consists of recompression to 165 feet (6 ATA) for a period of 15 to 30 minutes, followed by ascent to 60 feet (2.8 ATA) at 25 feet per minute where Treatment Table 5 or 6 is then employed. The period of exposure time at maximum depth is dependent upon the rapidity of resolution of symptoms and signs. Treatment Table 6 is used following an exposure at 165 feet exceeding 15 minutes duration.

GENERAL EFFECTS OF EXPOSURE TO OXYGEN THERAPY SCHEDULE

Data was acquired on the results of treatment of cases of decompression sickness and air embolism with the provisional format and subsequent modifications, contributed by nine reporting activities on standard NAVMED Form 816, "Report of Decompression Sickness and All Diving Accidents." Cases of altitude decompression sickness treated by these activities have also been reported.

Timed vital capacity and maximal mid-expiratory flow rate were determined before and after exposure to the 285 minute schedule (Table 6 of Figure 1), of nine test subjects. A carefully balanced, chain-compensated 13.5 liter spirometer (Warren E. Collins Co.) equipped with a large-bore directional breathing valve and 1.5 inch I. D. smooth bore hoses was used for these tests. Preliminary clinical and roentgenographic

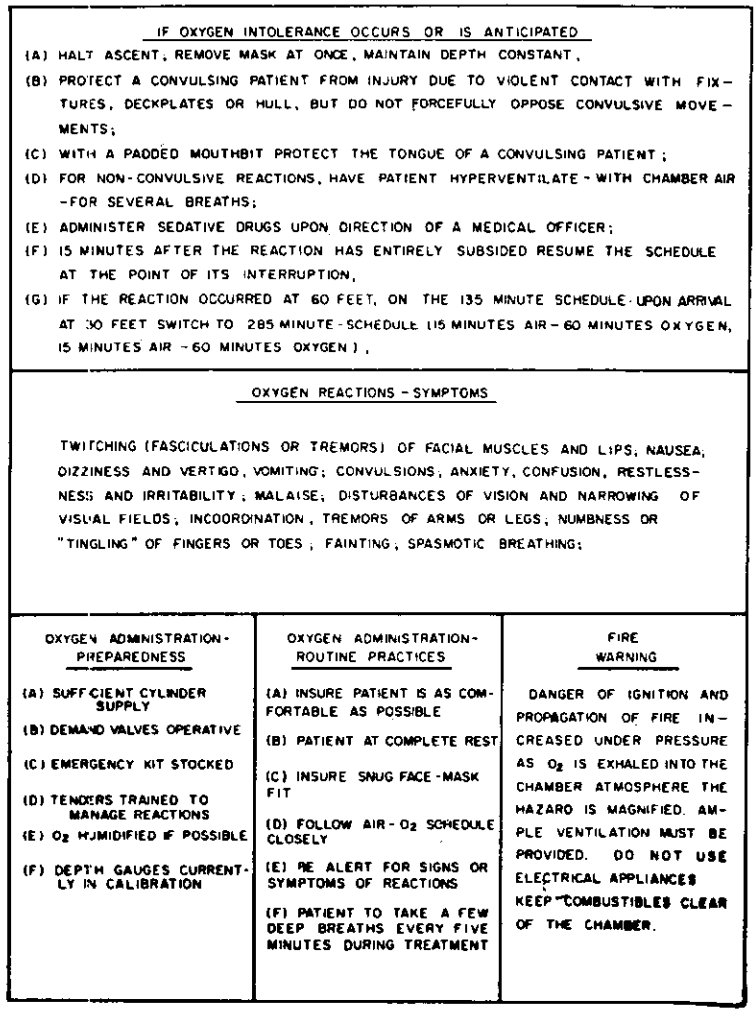

Fig. 2. Oxygen administration: rules, routines, reactions and precautions.

examinations of lungs and thorax were conducted for the nine test subjects.

Apical pulse rate and respiratory frequency were monitored, respectively with precordial leads from a Sanborn model 350-3200 EKG preamplifier and a Statham PR 23-ID-300 temperature-compensated 5 cm Hg differential pressure transducer which detected pressure changes within the face mask. Amplification was by a Sanborn 350-1100 carrier preamplifier, and recording with a Sanborn model 964 hot styllus oscillographic recorder.

Oxygen was breathed by subjects using face masks (M. S. A. Aviation Type) from which aliquots were sampled intermittently via a regulating valve system to sea level pressure and analyzed with a Beckman Model F3 paramagnetic oxygen analyzer. Readout of the analysis data was performed with an Esterline-Angus Model AW recording DC milliammeter.

Simulated depth (pressure) of the treatment chamber was determined with accurate Wallace and Tiernan Model FA 234 bourdon-tube depth gauges equipped with calibrated dials graduated in one foot (sea-water, S. G. 1.025, 25° C) increments.

Adequacy and safety of the air decompression exposures of the tenders was predicted by modified Haldane computational methods as described by Workman.[10]

TABLE I. DIVER-EXPOSURE-TREATMENT FACTORS

		Military	Civilian
Age Range (years)	20-30	58 (53%)	16 (40%)
	31-40	47 (43%)	19 (46%)
	41-50	5	3
	over 50	0	2
		N=110	N=40
Gas Mix Breathed	Air	52 (47%)	38 (95%)
	HeO_2	40 (36%)	1 (2.5%)
	$He\text{-}N_2\text{-}O_2$	16	1
	$N_2\text{-}O_2$	2	0
Maximum Depth (ft.)	0-100	14 (13%)	15 (37.5%)
	101-200	32 (29%)	23 (56.5%)
	201-300	38 (34%)	1
	301-400	22 (20%)	1
	401-500	4	
Total Bottom Time (Min.)	0-30	52 (47%)	11 (27%)
	30-60	21 (19%)	6 (15%)
	60-120	13 (12%)	14 (35%)
	120-240	5	6
	240-480	7	2
	480-720	10	0
	720-1440	2	1

TABLE II. DIVER-EXPOSURE-TREATMENT FACTORS

		Military (N=110)	Civilian (N=40)
Appearance of Symptoms (Min.)	under pressure	30 (27%)	12 (30%)
	0-30	28 (25%)	22 (55%)
	30-60	10 (9%)	2 (5%)
	60-120	15	0
	120-180	10	0
	180-360	11	3
	over 360	6	1
		42 of 150 cases had onset of symptoms under pressure (28%)	
Symptoms and Signs	Pain Only	70 (64%)	6 (15%)
	Pain plus motor or sensory	21 (19%)	29 (72%)
	Motor Only	3	0
	Sensory Only	14	0
	Motor and Sensory Only	2	5
		74 of 150 cases had serious symptoms (49.5%)	
Time From Onset To Treatment (Min.)	0-30	42 (38%)	3 (7.5%)
	30-60	13 (12%)	1 (2.5%)
	60-120	9 (8%)	5 (12.5%)
	120-180	7	5
	180-360	7	11
	360-720	0	7
	720-1440	0	5
	24-48 hrs.	0	2
	over 48 hrs.	0	1
Treatment Table Used	5	66 (60%)	11 (27.5%)
	6	44 (40%)	26 (65%)
	6A	0	3 (7.5%)

Exposure of Normal Subjects

There were no subjective manifestations of oxygen toxicity in the nine subjects exposed to Table 6 (Figure 1). The prolonged periods of continuous face-mask application did not produce reportable discomfort. No symptoms related to pulmonary irritation followed these exposures, nor was there any objective evidence of decreased pulmonary function. Post-exposure vital capacity and one-second timed vital capacity showed no significant change from pre-exposure values for any of the 9 subjects. The mean difference of post-exposure apical pulse rate was 14 per minute less than the pre-exposure value, with a range of minus 4 to 31 beats per minute. Lung fields remained normal as determined by clinical auscultation; post-exposure roentgenograms were not obtained.

Average gas analysis results obtained during steady-state exposures at 60 feet (2.8 ATA) were the following:

Sample Source	FO_2	Po_2 (mm Hg)
Within face mask	98	2020
Collected mixed-expired gas	95	2085
End-expired gas	89	1852

CHARACTERISTICS OF BENDS TREATED

Tables I and II present data relating to the divers incurring decompression sickness (military or civilian), the dive exposure, time of appearance of symptoms and signs and their nature, time delay until treatment was begun and treatment table used. Several of these factors bear on the severity of decompression sickness and the prospect for adequate treatment with complete disappearance of all signs and symptoms. The military population is compared to the civilian divers in that factors predisposed to severity of injury and less than optimum results of treatment have been evident in civilian diver patients treated with the U. S. Navy Treatment Tables.[4]

The civilian diver population studied was somewhat older than the military group, having 86% of a total of 40 divers in the age group to 40 years, compared to 96% for the military group of 110 divers. Nearly all (95%) of the civilian dives were conducted using air, while only 47% of the military dives were in this group. Few civilian dives were deeper than 200 feet, while 58% of military dives were between 200 and 500 feet in depth. While both diving groups

had nearly equal percentages of dives up to two hours duration (77 and 78%), military divers made 47% of their dives of 30 minutes or less duration, while for the civilian group this was only 27%.

Appearance of symptoms of bends under pressure as an indication of gross inadequacy of decompression, and a requirement for prolonged treatment procedures, occurred in nearly equal fractions of the military and civilian population reporting for treatment (27 and 30%, respectively). However, 85% of symptoms occurred in the civilian group within 30 minutes of surfacing, while only 52% of military divers had onset of symptoms at that time. Cases with early onset of symptoms are usually more severe and have a poorer prognosis for treatment.[6]

The military group had symptoms of pain alone in 64%, while this was only 15% for the civilian group. Among the civilians 72% had pain plus motor or sensory disturbances, while for the military group this combination occurred in only 19%. Since symptoms or signs other than pain require prolonged treatment on Table 3 or 4, it can be seen that the civilian case load would include 85% requiring such treatment, but only 36% of the military group.

Time from onset of symptoms or signs to beginning of treatment was one hour for 50% of the military group, while only 10% of the civilian group were under treatment at this time. Delay in treatment exceeding 6 hours occurred in 38% of the civilian group reported. Such delay in treatment after onset of symptoms relates to the outcome; the longer the delay, the poorer is the chance for relief of symptoms.[6]

The longer procedure of Treatment Table 6 was required for 65% of civilian patients, and for 40% of the military patients. The severity of decompression sickness occurring in both military and civilian divers is evident from the total of 74 of 150 cases (50%) with serious symptoms and signs, together with 42 of 150 cases (28%) in which onset of symptoms occurred while still under pressure. Thus, use of Treatment Table 3 or 4 would have been required in 116 of 150 cases (78%) in which Treatment Tables 5 or 6 were used.

RESULTS OF TREATMENT OF DECOMPRESSION SICKNESS

Treatment of Divers' Bends

One hundred fifty cases of decompression sickness occurring in 110 military and 40 civilian divers have been treated to date by recompression to 2 to 2.8 ATA with oxygen breathing. The results of this treatment are presented in Table III. Following the first treatment, 127 of 150 patients were free of symptoms, 8 had substantial relief, 5 had a substantial residual and 10 had recurrent symptoms. Military patients treated had relief of symptoms in 93%, civilian patients in 62%. Of the civilian patients with failure of initial treatment, 93% had serious symptoms; for the military patients this was 62%. Following a second treatment of 10 patients, 134 of 150 (89%) were completely free of all symptoms. In the remaining cases, substantial improvement occurred in 9 (5 civilian divers), leaving 7 of 150 patients (5%—all civilian divers) with substantial residual injury.

Treatment of Altitude Decompression Sickness

Table IV presents data relating to 7 patients incurring altitude decompression sickness that were treated with Treatment Tables 5 and 6. Altitude exposure inducing symptoms ranged from 18,000 to 43,000 feet. Five of the 7 cases treated had motor and sensory involvement. Onset of symptoms during altitude exposure ranged from less than 30 minutes to 7 hours, while one patient did not manifest symptoms until 30 minutes after return to ground level. Onset of treatment following symptoms exceeded 1 hour in 6 patients, and was greater than 7 hours in 4 patients.

TABLE III. RESULTS OF FIRST TREATMENT OF DECOMPRESSION SICKNESS

	Total (N=150)	Military (N=110)	Civilian (N=40)
Relief Complete	127 (84.7%)	102 (92.6%)	25 (62.5%)
Relief Substantial	8 (5.3%)	4 (3.7%)	4 (10.0%)
Residual Substantial	5 (3.3%)	0 (0.0%)	5 (12.5%)
Recurrent Symptoms	10 (6.7%)	*4 (3.7%)	*6 (15.0%)
*Treated at 33 feet only	5 (3.3%)	4 (3.7%)	1 (2.5%)
FAILURE OF INITIAL TREATMENT			
	Total	Military	Civilian
Total Cases	23 (15.4%)	8 (7.3%)	15 (37.5%)
Pain Only	4 (17.4%)	3 (37.5%)	1 (6.6%)
Serious Symptoms	19 (82.6%)	5 (62.5%)	14 (93.4%)
RESULTS OF SECOND TREATMENT			
	Total	Military	Civilian
Relief Complete	134 (89.3%)	106 (96.3%)	28 (70%)
Relief Substantial	9 (6.0%)	4 (3.7%)	5 (12.5%)
Residual Substantial	7 (4.7%)	0 (0.0%)	7 (17.5%)
Recurrent Symptoms	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number Retreated	10 (6.7%)	4 (3.7%)	6 (15%)

TABLE IV. TREATMENT OF ALTITUDE DECOMPRESSION SICKNESS EXPOSURE-TREATMENT FACTORS

Age Range	20-30	5	N=7
	31-40	1	
	41-50	1	
Site of Exposure	Altitude Chamber	6	
	In Flight	1	
Altitude Exposure (Ft.)	18,000	1	
	25,000-30,000	3	
	35,000	2	
	43,000	1	
Symptoms and Signs	Pain Only	2	
	Pain Plus Motor or Sensory	3	
	Motor and Sensory Only	2	
Appearance of Symptoms	0-30 min.	3	
	31-60 min.	1	
	61-150 min.	1	
	7 hrs.	1	
	30 Min. Post-Flight	1	
Time From Onset To Treatment (Hrs.)	0-1	1	
	1-4	2	
	7	2	
	14	1	
	48	1	
Treatment Table Used	5	4	
	6 extended	3	
Results of Treatment			
Complete Relief		5 (72%)	
Relief Substantial		1 (14%)	
Residual Substantial		1	
Complete Relief in 3 Days		7	

Extended treatment time on Treatment Table 6 was required for 3 cases. Five patients (72%) had complete relief of all symptoms and signs following initial treatment. One patient had substantial improvement, and 1 patient had a substantial residual effect upon completion of treatment, but in the following 3 days had complete resolution of all symptoms and signs.

Treatment of Traumatic Air Embolism

Results of treatment of 24 cases of traumatic air embolism are presented in Table V. Seventeen cases reported occurred during buoyant ascent training for submarine escape at U. S. Navy facilities. Five occurred in scuba diving, and one case resulted from explosive decompression in aircraft flying at 43,000 feet. All 24 patients had motor or sensory impairment, and 9 patients had pain in addition. Symptoms appeared during ascent or upon reaching the surface in 16 patients, while onset was delayed from 16 to 30 minutes in 2 patients. Time from onset to treatment was immediate in 9 cases, and less than 10 minutes in an additional 8 cases. The remaining 7 patients had delay in treatment from 30 to 600 minutes. Treatment tables 5 and 6 were used to treat 7 patients, Table 5A for 12 patients, and Table 6A for 5 patients. Complete relief of all symptoms and signs following treatment was attained in 18 of 24 patients (75%). Residual symptoms occurred in 3 patients, and recurrence of symptoms in another 3 patients. Additional treatment was given the 3 recurrences, with complete relief resulting in all 3 cases for a final result of 21 patients (87%) returned to complete freedom from symptoms. Complete recovery of function followed over a 10 day period in the 3 patients with residual effects after treatment.

TABLE V. TREATMENT OF TRAUMATIC AIR EMBOLISM

Number of Cases Treated	Military	22	N=24
	Civilian	2	
Type of Exposure	Buoyant Ascent	17	
	Dry Chamber Ascent	1	
	Open Water	5	
	Explosive Decompression in Aircraft	1	
Symptoms and Signs	Pain Plus Motor or Sensory	9	
	Sensory Only	1	
	Motor Only	3	
	Motor and Sensory	11	
Appearance of Symptoms (Min.)	Upon Reaching Surface	16	
	0-15	6	
	16-30	2	
Time From Onset To Treatment (Min.)	Immediate	9	
	0-10	8	
	30-60	4	
	60-300	1	
	300-600	2	
Treatment Table Used	5	3	
	5A	12	
	6	4	
	6A	5	
Results of Initial Treatment	Complete Relief	18	(75%)
	Residual Symptoms	3	(12.5%)
	Recurrent Symptoms	3	(12.5%)
Results of Second Treatment	Complete Relief	21	(87%)
	Relief Substantial	3	(12.5%)
	Recurrent Symptoms	0	
	Complete Recovery in 10 Days	24	

APPRAISAL OF OXYGEN TREATMENT METHOD

A minimal recompression method, with air breathing by the patient, was developed and applied during the construction of the Dartford Tunnel.[3] It proved to be eminently successful in treating cases of severe decompression sickness, though as with treatment of naval divers, prompt recompression was usually possible. Their approach to the problem was "to keep the therapeutic pressure as low as possible to minimize any contribution which absorption of nitrogen during the recompression itself may make to recurrence of the lesion." Slow decompression and stages require a total treatment time comparable to U. S. Navy Treatment Tables 3 and 4.

Studies of resolution of gas bubbles have been reported by Wyman, et al.[11] and Van Liew.[8] Wyman's data indicate that the lifetime of an air bubble of given size should not vary appreciably with pressure greater than 3 ATA. Van Liew gives evidence that the rate of diameter reduction for an air bubble in tissues of an oxygen-breathing patient should be 4 to 5 times greater than with air breathing at 3 ATA, at which pressure the maximal rate of diameter reduction for air breathing occurs. The gas tension gradient from bubble to tissue is maintained optimally throughout the entire time course of the oxygen-breathing period; therefore, reductions of ambient pressure are unlikely to permit bubble growth through attainment of osmotic equilibrium of bubbles with supersaturated tissue-fluid inert gases. However, when air is breathed during therapeutic recompression, bubble growth by this mechanism may occur.

Persistence of neurological symptoms, usually indicative of spinal cord injury, can occur subsequent to improper decompression from prolonged or repeated exposure to pressure. Weakness, paresis and paralysis of muscle groups, impairment of urinary bladder and bowel function have frequently been unresponsive to recompression therapy when such treatment has been delayed. Tissue edema and hemorrhage resulting cannot be resolved solely by recompression. Circulatory impairment of injured tissues constitutes a relative contra-indication to air saturation recompression. Oxygen breathing at increased pressure is specific therapy aimed at providing adequate oxygenation of tissues injured by hypoxia to promote recovery of function. With bubble resolution and restoration of circulation to injured tissues accomplished, patients in whom residual damage is manifest can be cared for properly in a hospital setting rather than being required to remain incarcerated in the recompression chamber. The decreased obligation of treatment time, and numbers of personnel required to provide this, will be significant as this bears on ability to meet operational mission requirements for activities concerned.

The specific goal of accomplishing complete return to normal function of all severely injured divers by the use of Treatment Tables 5 and 6 is not attained, as evidenced by the results stated in Tables I and II. While the goal is desirable, it may be unattainable

in view of the gross inadequacy of decompression frequently encountered, the resulting severity of injury of vital tissues, and the prolonged delay before treatment has been instituted in many cases. The result of initial treatment, which produced complete relief in 85% of 150 patients, is a considerable improvement over the 55% success of Treatment Tables 3 and 4, which would have been required in 78% of the cases treated.

The final result following a second recompression of 10 patients was complete relief of symptoms in 96% of military patients and 70% of civilian patients. Seven patients (5%) of a total of 150 treated for decompression sickness were left with a substantial residual injury. Adjuvant drug therapy, including intravenous fluids, dexamethasone and papaverine, was administered in these patients in an attempt to improve circulation to injured tissues and combat tissue edema. Little improvement was seen to result. Three civilian patients were treated on Table 6A with recompression to 165 feet (6 ATA) without additional benefit resulting from greater pressure. Follow-up reports available on 4 of 7 patients left with a substantial residual injury indicate that in only one case has a return to normal activity resulted.

Results of treatment provided 7 cases of altitude decompression sickness are judged to be adequate with 5 patients obtaining complete relief of symptoms and 1 additional patient substantially improved. Full recovery followed over a 3-day period in the remaining patient. Five patients had nervous system impairment, and 4 had delay in treatment of 7 hours or more to further jeopardize the success of treatment.

Treatment of 24 patients with traumatic air embolism proved satisfactory with an ultimate result of 87% showing complete relief of symptoms, after treatment of 3 recurrences following the first treatment. An earlier and less adequate treatment format was used for some of the patients. The present format of Treatment Tables 5A and 6A should reduce recurrences somewhat.

CONCLUSIONS

The standard U. S. Navy recompression procedures for treatment of decompression sickness using compression while breathing air, provide reliable schedules for those divers stricken subsequent to pressure exposures conducted with reasonable caution and conservatism. They are, in general, not adequate for successful management of severely injured patients following grossly inadequate decompression and delay in institution of recompression. The rising incidence of complicated and difficult recompression experiences can be related to particular segments of the diving casualty population. The minimal-pressure oxygen-breathing method has provided a successful means of treating severe decompression sickness resulting from conventional diving, saturation exposures, altitude ascents and repetitive diving. A modification of this method has also proven successful in treatment of cases of traumatic air embolism.

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THE TREATMENT OF COMPRESSED AIR ILLNESS UTILIZING OXYGEN*

O. D. YARBROUGH AND A. R. BEHNKE

Experimental Diving Unit, Navy Yard, Washington, D. C.

COMPRESSED air illness refers to those symptoms produced by emboli formed as a result of too rapid decompression from high pressure atmospheres of air or mixtures of helium and oxygen. It is the purpose of this paper to present the essential data with regard to past and present treatment methods with special reference to a procedure we have employed at the Experimental Diving Unit, Navy Yard, Washington, D. C.

Briefly, the major symptoms of compressed air illness are pain, asphyxia and paralysis, occurring singly or in combination. Minor symptoms which may or may not be followed by serious sequellae are itching, skin rash and fatigue. These symptoms arise primarily from obstruction of blood flow by gas bubbles accumulating in the peripheral and pulmonary vascular beds to produce tissue ischemia. That bubbles form primarily in the blood stream and tend to accumulate in the veins has been repeatedly observed. In dogs rapidly decompressed from high pressures and showing massive gas embolism, the lymphatic trunks were singularly free from bubbles while the accompanying veins presented the beaded appearance characteristic of gas in blood vessels (1).

The relief afforded patients by a return to compressed air was recorded as early as 1854 by Pol and Watelle (2). Davis (3) aptly describes the appropriateness of recompression by stating that, "No one, who has seen the victim of compressed air illness, gravely ill or unconscious put into a chamber and brought back to life by the application of air pressure, will forget the extraordinary efficiency of recompression, or be backward in applying it to a subsequent case of illness."

It follows then, that the prime requirement in treatment is the rapid restoration of normal blood supply by compression and absorption of obstructing gas emboli. That this practice has a sound theoretical basis is evidenced by the fact that a gas bubble decreases in size in accordance with Boyle's law (4). For example, at a pressure of 75 pounds gage (6 atms. absolute) the size of a bubble will have decreased 84% from the application of pressure alone.

Although recompression has become the accepted method of treatment, there has been striking disagreement as to the manner of its application. It is recognized, however, that the effectiveness of recompression is related to the promptness with which it

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The material in this article should be construed only as the personal opinion of the writers and not as representing the opinion of the Navy Department officially.

is applied. Keays (5) particularly, was convinced that the benefits resulting from recompression were definitely dependent upon the promptness of treatment. Langlois (6) believed also that rapid intervention was indispensable in preventing prolonged anemia of the nervous centers resulting in persistent lesions. In addition, Bornstein (7) thought that delay in recompression necessitated the use of increased amounts of pressure for symptomatic relief.

In keeping with this principle of early treatment it is essential that divers remain in the immediate vicinity of the recompression chamber for at least 12 hours following exposure; certainly they should not be further removed than 1 hours' travel time for this period. All patients, moreover, despite the elapsed time since the onset of symptoms, should receive a recompression trial. Occasionally symptoms are aggravated by recompression at the lower pressures but usually the symptoms will disappear if sufficient pressure is applied.

With regard to the amount of pressure necessary, four different methods are listed under the following headings:

(a) Sufficient pressure to relieve symptoms.
(b) Employment of pressure greater than that required for relief.
(c) Return to the pressure of the original dive.
(d) Greater pressure than that corresponding to the original dive.

Since the amount of gas in bubble form is unknown at the time of recompression, irrespective of the previous diving depth, headings (c) and (d) may be eliminated from further consideration. Relief of symptoms in our experience serves as the basic criterion in determining the amount of pressure to be applied.

In the mild cases of compressed air illness, comparatively low pressures (30 pounds gage) afford relief. In dogs even after massive embolism was produced, the application of 30 pounds pressure relieved the circulatory and respiratory symptoms and caused a complete disappearance of bubbles visible to the unaided eye. Nervous tissue damage, however, was not prevented by this low pressure, since reappearance of circulatory and respiratory symptoms, and massive embolism, indicated that negligible amounts of gas in bubble form had been eliminated during the low pressure exposure. In order to prevent nervous tissue damage (primarily in the spinal cord with its poor blood supply) the practice was developed of raising the pressure immediately to 75 pounds gage.

Taking these facts into consideration it has been our practice to apply pressure until all symptoms are relieved and in addition, to add one more atmosphere in the effort to restore completely blood supply to the affected tissues. Our minimum pressure for recompression however, is 45 pounds per square inch equivalent to a diving depth of 100 feet. For example, if relief should occur at 50 feet,* the pressure is arbitrarily increased to the equivalent pressure at a depth of 100 feet because we feel that the 75% reduction in bubble size at 100 feet as compared with the surface promotes a more rapid elimination of gas and

*Diving depth and pressure are used interchangeably in this paper. A pressure of 1 atmosphere (14.7 lb. per sq. in.) is equivalent to a depth of 33 ft. of sea water.

tends to prevent incipient lesions in the spinal cord.

On the other hand, we feel that there is little to be accomplished by raising the pressure above 75 pounds, equivalent to a depth of 165 feet. At this pressure or depth the size of the bubbles has been reduced five-sixths of their surface volume; higher pressures can do little to improve circulation and would delay considerably the return to a depth at which oxygen could be breathed. Were it possible to obtain the resolution of all the gas in bubble form, then exceedingly high pressures would be justified. But unfortunately by the time the serious cases are recompressed, so much gas has diffused from the tissues into the blood stream that the capacity of the blood stream for absorbing gas has been exceeded at practicable pressures, i.e., below 10 atmospheres. For the complete elimination of gas emboli we rely upon the use of oxygen at comparatively low pressures.

The next consideration is the duration of time to be spent at maximum depth. We have made a practice of keeping our patients for a minimum of 30 minutes at the maximum depth of 165 feet. During this period of time all of our patients showed complete symptomatic recovery. This amount of time is in harmony with the recommendation of Bornstein that 20 to 30 minutes be maintained at the highest pressure before starting decompression. As to the maximum period of time for staying at the highest pressure, Davis (3) believes that it is useless to wait longer than 2 hours if the patient has not been cured in that period of time.

Our experience has been that those patients who respond to pressure treatment, do so rather promptly. A few patients, however, show only slight improvement when as much as 75 pounds pressure has been applied. If in the treatment of these patients the stay at 75 pounds is continued, improvement usually takes place. It can be stated empirically that as long as improvement occurs the maximum pressure should be maintained for a period of at least 2 hours.

Having accomplished symptomatic recovery with the patient exposed to maximum pressure, it is now necessary to bring about the reabsorption and elimination of gas in bubble form while bringing the patient back to normal pressure. Prior to 1937 we completed this part of the treatment schedule according to the scale in table 1. These tables were calculated according to the principles outlined by Boycott, Damant, and Haldane (8) for the elimination of gas held in a state of supersaturation by the body tissues. It was assumed for example, that the slowest desaturating part of the body was in complete equilibrium with a pressure equivalent to the various depths enumerated in table 1.

The time periods listed at the different steps were so arranged that the pressure of gas in the tissues never exceeded a ratio of 2:1 compared with the gas pressure in the environment. While such a table has been applicable for bringing divers to the surface from the depths under consideration by Haldane and his co-workers, the applicability of such a schedule for removing gas in bubble form from the blood stream may well be questioned.

In 1937 we simplified and shortened the previous treatment table by em-

ploying oxygen therapy at a level of 60 feet or less. The experimental basis and rationale for the principles underlying this method of treatment were developed by Behnke and Shaw (1). Figure 1 represents a modification of their treatment outline to include the tested principles underlying the data in table 1.

Usually the ascent to 60 feet can be made at the rate of 25 feet per minute after remaining at a depth of 165 feet for 30 minutes. Oxygen inhalation is begun upon reaching the 60 foot level and is continued for 1½ hours, during which period the return of the patient to normal pressure proceeds as shown on the treatment outline (fig. 1).

We have successfully applied this treatment in 50 cases of helium and oxygen "bends." The characteristic symptoms exhibited by the patients prior to treatment were pain usually in the extremities, skin rash, cyanosis, dyspnea, and the "shock" syndrome. We feel that it is needless to go into a detailed discussion of symptomatology. It suffices to say that many of our patients showed symptoms enumerated in the beginning of this paper as characteristic of large amounts of gas in bubble form in the blood stream. Whether or not a particular tissue will be affected and to what part of the body symptoms will be referred is probably dependent upon the extent of collateral circulation to tissues and the chance location of the emboli.

It should be remarked that pure oxygen breathed at 60 feet has been well tolerated by all patients. A somewhat higher pressure of oxygen could be breathed (Behnke et al., 9), but we have found that oxygen therapy begun at 60 feet and reaching the 30 foot level after a period of 1½ hours was sufficient to afford permanent relief to 49 of our 50 patients.

TABLE 1

DECOMPRESSION SCHEDULE

	DEPTH														TOTAL
	140	130	120	110	100	90	80	70	60	50	40	30	20	10	
															minutes
100											14	42	52	68	175
150									22	30	35	42	52	68	249
200						7	22	24	26	30	35	42	52	68	306
250				13	13	19	22	24	26	30	35	42	52	68	351
300	4	14	16	16	13	19	22	24	26	30	35	42	52	68	387

The time saving factor over our previous regime using air (table 1) has been about 45%.

If the treatment outlined in figure 1 fails to afford permanent relief, the patient is again returned to the pressure level at which relief of symptoms occurs. This pressure is invariably low (under 30 pounds or less than 66 feet) and is maintained for a period of 12 to 24 hours followed by a gradual decompression to the surface. This latter decompression is accomplished on the 100 foot scale in table 1. This practice has been referred to as the "overnight soak" and because of its

simplicity and effectiveness, forms the conclusive method of terminating treatment for compressed air illness.

In commenting on the outline of treatment shown in figure 1, it may be feasible to conduct the entire oxygen breathing period at the 60 foot level, instead of during stage decompression to the surface. It is apparent that minute bubbles which remain following decompression from 165 feet to the 60 foot level could be prevented from reaching any harmful size by maintaining the pressure at the latter level. A threefold increase in the size of bubbles would occur if the patient were immediately brought to the surface from the 60 foot level (approximately 3 atmospheres absolute).

Moreover, because of the increased gas carrying power of the blood, a greater amount of gas should be eliminated at the 60 foot level per unit of time in comparison with the gas elimination at lower levels. With a pressure head of one atmosphere, 30 to 50 cc. of inert gas are eliminated per minute by an individual breathing oxygen. With a pressure head of 3 atmospheres, it is estimated that about 100 cc. per minute would be eliminated by the body.

In view of these considerations, we have tested the feasibility of breathing oxygen for 1½ hours at the 60 foot level. Following this period of time, the patient, continuing to breathe oxygen, is slowly returned to normal barometric pressure at the rate of 10 feet per minute.

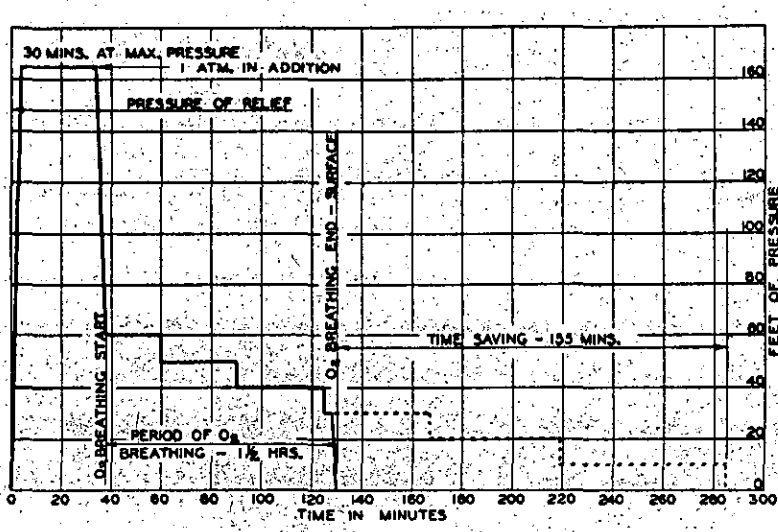

FIG. 1.

The number of cases treated in this manner are too few for us to draw any conclusions; however, to date no complications following this treatment schedule have occurred.

In conclusion reference may be made to the use of oxygen-nitrogen, or oxygen-helium mixtures for use at pressures above 30 pounds (the safe limit of oxygen tolerance), or in depths

in excess of 66 feet. While theoretically such mixtures might shorten decompression time, we have had such favorable results with the treatment outlined in this paper that the use of gas mixtures has been dispensed with.

It might be well to have a 50-50 oxygen-helium or oxygen-nitrogen mixture available for administration to a moribund patient at a pressure of 75 pounds, but the efficacy of such therapy remains to be tested. The procedure of placing a patient on pure oxygen after an initial 30 minutes' exposure on the bottom (165 ft. or less), constitutes our basic therapy because of its simplicity and effectiveness.

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PULMONARY FUNCTION

Articles selected by Robert Gelfand, M.E.
Institute for Environmental Medicine
University of Pennsylvania

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PULMONARY FUNCTION

Articles selected by ROBERT GELFAND, M.E.
Institute For Environmental Medicine
University of Pennsylvania, Philadelphia, PA

Pulmonary function in the context of the selection of seminal documents in undersea medicine emphasizes limitations imposed upon ventilation by exposure of healthy men to the elevated inspired gas densities associated with exposure to increased ambient pressure. Fundamental work by Rohrer (1925) in describing the mechanical properties of the respiratory system is still widely cited today. That the lungs and pulmonary tract themselves are not passive in respiration is also of basic importance in undersea activity; this critical aspect of exposure to pressure is well represented by the concept of effort-independent expiratory flow limitation as described by Mead et al. (1967).

The effects of the inevitable elevation of gas density in increasing resistance to gas flow and work of breathing while decreasing pulmonary ventilatory capacity were recognized early by several investigators as limiting factors during physical exertion in the deep undersea environment. Albano summarized his own pioneering work as well as that of others in an exceptionally clear description in 1967 (English translation, 1970). In a systematic study covering differing lung volumes and multiple gas densities (to approximately 10 grams/liter), Wood and Bryan (1969) defined the nonlinear relationship between maximum pulmonary flow rates and increase in pulmonary resistance associated with progressive elevation of gas density.

Studies of pulmonary mechanical functions during voluntary maneuvers are vital for analysis of factors limiting flow and are useful in prediction of exercise ventilatory capabilities but cannot substitute for actual measurement of ventilation and gas exchange during physical work. Interpretation of studies in compressed air and nitrogen/oxygen are complicated by effects of narcosis and hyperoxia. Physiological limits of gas flow due solely to density must be investigated in dry chambers using non-narcotic gases such as neon/oxygen and helium/oxygen at relatively high pressures.

Between 1965 and the present, a number of investigations of physiological responses to exercise in helium/oxygen filled chambers at increasing depths have been reported. An early effort was by Hamilton at 650 FSW described in 1967. A surge of activity to 1000 FSW in the latter part of the 1960's is reflected by the papers in Part VIII of the Proceedings of the Fourth Symposium on Underwater Physiology (1971) with contributions by Miller, Wangensteen and Lanphier; Bradley et al.; Salzano, et al.; and Schaefer, Carey, and Dougherty. These exposures and successive ones to even greater pressures were dramatic in terms of the depth equivalents achieved, but hardly so in terms of increase in respiratory flow resistance. The gas density of 0.3 ATA O_2 in He at 1600 FSW is about the same as compressed air at 200 FSW.

For prediction of actual limits of human tolerance due to gas density and respiratory work, a safe actual maximum depth of 1200 FSW was used with He, N_2 and Ne in "Predictive Studies III—1971" to simulate the pulmonary flow resistance which would be encountered with He/O_2 at pressures of 400, 700, 900, 1200, 2000, 3000, 4000 and 5000 FSW (Lambertsen et al., 1977). Extreme work was possible for limited intervals even at the 5000 FSW equivalent depth. Subsequently, choking dyspnea was reported during underwater exercise at 1600 FSW (Spaur et al., 1977), while vigorous practical work underwater was reported with no untoward effects at 1600 FSW in "Predictive Studies IV—1975" (Lambertsen et al., 1978). Thus it is as yet uncertain whether physiological limits of work tolerance determined in dry chambers can be reached during actual immersion in the water, and whether or not effects of pressure itself on excitable tissues may interact disadvantageously with mechanical effects of high gas density.

A synthesis of probable respiratory decompensation as a consequence of chronic exposure to pulmonary and related stresses imposed by extreme pressures is offered in an anlysis by Lambertsen (1981).

PULMONARY FUNCTION

ROBERT GELFAND

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Albano G.: Ventilatory mechanics. (Pt A of Ch IV: Hyperbaric Respiration) in *Principles and Observations on the Physiology of the Scuba Diver*. Transl. from Italian, ONR Report DR-150, 1970, p. 69–91. References on p. 129–132.

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ONR Report DR-150

Principles and Observations on the Physiology of the Scuba Diver

(Principi ed Osservazioni di Fisiologia del Sommozzatore)

GASPARE ALBANO

International Laboratory for Underwater Medicine
Palermo, Italy

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A) Ventilatory mechanics.

The mechanics of ventilation in hyperbaric conditions has received the attention of numerous studies, from the oldest by von Vivenot to the most recent by Albano, Bühlmann, and Wood.

The primary effect of increased external pressure on the respiratory apparatus is a lowering of the diaphragm with increased vital capacity (von Vivenot), caused by depression in the abdominal cavity (Aggazzotti). Decompression, however, causes opposite phenomena (Aggazzotti; Albano and Indovina).

The lowering of the diaphragm obviously eases inspiration, and expiration is caused by greater elastic tension accumulated during inspiration. Another important effect consists of the increase in respiratory resistances due to the increased density of gases (Albano; Bühlmann; Wood). Both contribute to create an increase in intrapleural negativity, both in inspiration and expiration (although less regular), which was seen in animals during compression (Aggazzotti and Lenzi). In man, Schilling and coworkers found a 6.5-percent increase in vital capacity, in addition to an increase in expiratory pressure up to a maximum of 13.05 percent. Therefore, it appears important, in the first instance, to determine the extent of change in vital capacity in order to derive from it the necessary consequences regarding respiratory function.

Zannini and coworkers have observed an average increase of about 13 percent at a pressure of 4 atmospheres absolute. Nevertheless, the formula on which VC variation depends is easy to derive. In the case of our standard subject (with body surface of 1.85 square meters), the vital capacity, according to West, at ground level will be:

$$1.85 \times 2.5 = 4.625 \text{ liters}$$

according to 77 percent of a thoracic volume totaling about 6 liters.

Data from anatomical literature (Testut and Jacob) show that the surface of the diaphragm (always in average conditions) is 270 square centimeters, so that for every centimeter of the lowering of the diaphragm there will be a corresponding increase in thoracic volume of about 270 cubic centimeters and a VC increase of

$$0.77 \times 270 = 207.9 \text{ cc.}$$

It appears evident, therefore, that in order to arrive at the VC increase amount, it is necessary to know the difference between diaphragm height and, therefore, the extent of reduction in abdominal volume. This depends on its gas content which, at atmospheric pressure (as can be observed from common radiological routine) is about (considering individual differences and time) 10 percent of the average gastrointestinal volume, and we will use this percentage as standard.

According to anatomical literature, we may assume the following volumes for our standard subject:

	Cubic centimeters
Stomach	1,200
Duodenum	100
Fasting-ileum . .	260
Cecum	250
Colon	1,440
	3,250

The abdominal gas content is, therefore, 325 cubic centimeters.

Because the abdominal cavity can be compared to an ellipsoid, its volume, V, will be:

$$V = 4\pi abc/3$$

where a, b, c are the semiaxes of the ellipsoid. After establishing the appropriate proportion between external and internal diameters, excluding the superficial tissues, and considering that the diaphragmatic cupola is forced upward above the xiphoid appendix, we can establish the following (from data by Castaldi and Vannucci): height, 46 centimeters; transverse axis, 20 centimeters; and anteroposterior axis, 11 centimeters. Thus, for the three semiaxes we have: $a = 23$ centimeters; $b = 10$ centimeters; and $c = 5.5$ centimeters. Therefore, V will equal 5,300 cubic centimeters.

This volume is the sum of intestinal gas content and the remaining abdominal content:

$$V = 4,975 + 325 = 5,300 \text{ cc.}$$

Every difference in diaphragm level (dh) is double the difference between a and a'; that is,

$$dh = 2\,(a - a')$$

whereas, from geometry, we have:

$$a = \frac{3\,V}{4\pi bc}$$

At an environmental pressure of 4 atmospheres absolute the intestinal gas volume will be reduced to 325/4 = 81 cubic centimeters, with a total volume reduction in the abdominal cavity of:

$$V = 4.975 + 81 = 5,056 \text{ cc,}$$

where:

$$a' = (3 \times 5,056)/(4\pi \times 55) = 21.85 \text{ cm;}$$

then:

$$dh = 2\ (23.00 - 21.85) = 2.3\ cm.$$

Therefore, the total increase in pulmonary capacity will be:

$$270 \times 2.3 = 610\ cc.$$

From this we have a vital capacity increase of:

$$0.77 \times 610 = 469.7\ cc,$$

which is in extraordinary agreement with data experimentally obtained by Zannini and coworkers, who found increases varying from 260 to 860 cubic centimeters, with an average of 496.6.

At 10 atmospheres absolute the abdominal volume will be only 5,007.5 cubic centimeters, with $a' = 21.74$. The corresponding dh (2.5 centimeters) seems to be in excess if we consider the moderate deviations we (Albano and Indovina) found in the heart's position at this environmental pressure. However, it must be pointed out that they were carried out on subjects in a supine position, which reduces the anteroposterior axis of the abdomen rather than its height.* However, it must be considered that the supine position is unnatural for divers and, therefore, the theoretical calculation can be considered unquestionably valid.

It is of interest to be able to predict the size of increase in VC caused by high pressure as a percentage of the preexisting VC, postulating that VC constitutes 77 percent of the total pulmonary capacity (TC). Furthermore, we will consider that TC is in relation to the diaphragmatic surface and to other body measurements and, particularly, the volume of abdominal gas, and that those involved are generally subjects with normal measurements.

The VC variation, then, can be expressed in the following equation:

$$VC' = VC + \frac{77\ (dh \times sD)}{100} \qquad (IV,A,1)$$

where sD represents the extent of diaphragm surface.

Given:

$$dh \times sD = c \times VC,$$

Eq. (IV,A,1) becomes:

$$VC' = VC + \frac{77 \times c \times VC}{100} \qquad (IV,A,1a)$$

which presupposes that the diaphragm surface, the intestinal gas volume, the abdominal cavity, and the height of the abdominal cavity are related to VC (and,

*Rohrer (1916, believed that the weight of abdominal viscera presses against the diaphragm in this position. According to Rahn and coworkers, this would cause an increase of 7.5 mm Hg in elastic pressure of the chest, with a corresponding decrease in VC.

therefore, to each other) by a constant relationship in the various subjects. This, naturally, constitutes an abstraction that is valid only in carefully selected individuals.

Following our hypothesis and considering the abdominal volume at high pressure, V', to be equal to:

$$V - Vg + Vg'$$

(where Vg represents the volume of intestinal gas), the solution of c can be approximated by:

$$c = 1.82 - \frac{1.82}{H}$$

where H is the absolute pressure in atmospheres.

Table VIII gives all the values of the coefficients in Eq. (IV,A,1a), $77 \times c$, for the various environmental pressures up to a value corresponding to a depth of 100 meters. From the values given in Table VIII and knowing the initial value of VC, it is easy to find the value of VC' using Eq. (IV,A,1a). It must be said that the values found in this way are adapted perfectly to the numerical data from the preceding example. Agreement with experimental data furnished by the literature is a little less accurate, but here there is no agreement among the authors, even though all admit considerable individual and interindividual changes. For example, Zannini and coworkers have found a percentage increase of 13 percent at 4 atmospheres absolute, whereas Schilling and coworkers have found only 6.5 percent at 6 atmospheres absolute.* We feel our data should be understood as expressions of a very broad average of values with wide individual and interindividual variations, provided that the time lapse at high pressures before the data were recorded was not excessive.

TABLE VIII
Coefficients for Variation
in Vital Capacity at High Pressures

Depth (meters)	Pressure (ata)	77 x c
0	1	0.00
10	2	7.00
20	3	9.34
30	4	10.50
40	5	11.23
50	6	11.67
60	7	12.00
70	8	12.24
80	9	12.44
90	10	12.60
100	11	12.74

*A 10-percent increase was recently found even under 21 atmospheres in oxygen-helium (Hamilton et al.).

In fact, as was found by Aggazzotti on animals, and as we found in our studies on changes in the position of the heart during exposures at 10 atmospheres absolute (Albano and Indovina), during exposure the level of the diaphragm tends to return very slowly to normal conditions. This was due to a recovery of intestinal gas volume brought about by the same factors that initially created it (swallowing small quantities of air, intestinal fermentation, and so forth). However, it must be pointed out that this takes place over a very long time, which becomes even longer the greater the absolute pressure and the less the intensity of intestinal fermentation. We believe, in any case, that this recovery tendency is the principal cause of disagreement among the authors on the different time intervals between the beginning of compression and the moment the examination was made.

Figure 10 shows the volume-pressure diagram of the human chest and lungs during breathing by mouth (Rahn et al.). The ordinate shows the volumes ventilated in percent of VC, and the abscissa shows the pressures needed to move such volumes along the airways. The entire respiratory cycle occupies an area that expresses the amount of work done for breathing. The entire area of the graph results in 8.7 kpm, which is, theoretically, the maximum amount of work that can be done during a complete respiratory cycle.* In practice, this amount is never reached, for reasons we will discuss in detail later. For a good understanding of what we will say, however, it is necessary to stress at this time *some points that emerge from the volume-pressure diagram* (*Fig. 10*).

1. Positive pressures above 50 to 60 mm Hg, if developed when lungs are filled to capacity—or pressures over 80 mm Hg for lower lung volume—will cause air penetration through the connective tissue of the bronchioles (interstitial emphysema of the neck and mediastinum (Katz; Kronecker)) or through the interalveolar septa (traumatic aeroembolism (Pollak and Adams; Henry;

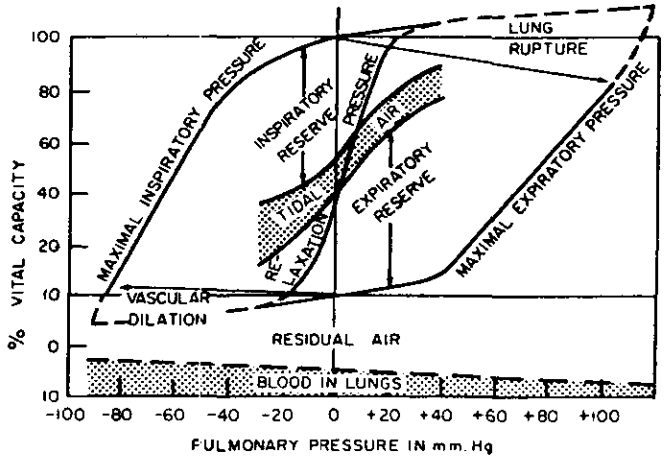


Fig. 10. Volume-pressure diagram of the human chest and lungs (from Fenn, 1951).

*If VC = 5 liters and PE + PI = 128 mm Hg = 0.168 atmosphere; then, maximum respiratory work (MRW) = 0.843 liter/atm = 8.70 kpm = 20.40 calories.

Lambert)). However, there is little strain on the lung when it is not markedly expanded, as during the process of defecation (Fenn).

2. Negative pressures above 80 mm Hg, developed in a residual volume state, cause overdilation of the pulmonary blood vessels, the possibility of endopulmonary hemorrhage, of cavity formation with air-fluid level (Ricci), or of acute heart dilation (Stigler). However, when the lungs are filled to capacity, it may be possible to breathe even under slightly higher negative pressures (12 mm Hg, according to McKay).

3. The volume of blood contained in the lungs changes in relationship to the degree of pressure developed during the respiratory cycle. It increases during inspiration and decreases during expiration. (According to Otis and coworkers (1945), about 200 to 250 cubic centimeters is expelled by the lungs at maximum positive pressure.) As a consequence, the volume of residual air and that of vital capacity undergo opposite fluctuations.

4. The volume-pressure curve for passive inspiration and expiration, called the "relaxation pressure curve," is S-shaped and crosses the vertical axis at a point that corresponds to the end of normal expiration (37 percent VC) and that refers to the resting position of pulmonary elasticity when the elasticity of the chest is excluded. The slope of this curve, at different pressures, indicates that the volume of equilibrium between pulmonary tension, which tends toward contraction, and chest elasticity, which tends toward expansion, is 94 cc/mm Hg (Rahn et al.).

5. The tidal volume (Fig. 10) encloses the lung volumes spontaneously selected when breathing against either a positive or a negative pressure of the value indicated on the abscissa. The upper margin crosses the vertical zero axis at 53 percent of VC, which indicates the state of equilibrium between the chest and the lung. The point at which the upper edge and the relaxation curve cross (62 percent of VC) indicates the resting position of the chest elasticity. The lower edge coincides where the vertical axis crosses with the relaxation pressure (37 percent of VC). This means that expiration of a volume between 53 and 37 percent of VC is entirely passive. Instead, inspiration becomes passive when breathing against a positive pressure of 9 mm Hg (Rahn et al.).

These data must not be forgotten. They have a certain importance because of their effect on the mechanics of hyperbaric ventilation. It has been demonstrated (Miles; Seusing et al.; Albano; Bühlmann) that respiratory resistance (and, therefore, the pressure necessary to overcome it) increases under high pressure.

As shown in Fig. 10, gas penetrates and leaves the lungs by a negative and positive pressure gradient that occurs, through breathing, between the pulmonary alveoli and the outside (alveolar-mouth gradient). This gradient permits us to evaluate the extent of respiratory work and the pressure exercised against the parenchymal elements. Various attempts have been made over the past 10 years to establish a relationship between gas density and the magnitude of respiratory work (McKerrow; Miles; Zannini et al.; Rossier and Bühlmann/ Cooper, but there have been conflicts between theoretical predictions and experimental

results (Fig. 11).* In effect, the exact relationship can only come from an accurate analysis of all the factors that pertain to breathing mechanics; relevant experimental data not only would not be defective, but would supply rather uniform results.

In reality, the dynamics of gas flow through the airways was exhaustively studied by Rohrer in 1915 (Fenn). Rohrer began his study by examining the flow of gas in a system of pipes. The movement of fluid through the tubes can be, as is known, either laminar or turbulent on the basis of the Reynolds number system. Using Biel's observations, Rohrer established that for pipes with a rather irregular flow course, such as the bronchial system, and for an alternating flow, it must be admitted that even in normal conditions a certain percentage of the resistance in the airways is due to the turbulent fraction. Therefore, the total pressure drop, p, can be derived from the sum of the losses due to the laminar flow fraction, p', and to those due to the turbulence fraction, p'', according to the formula:

$$p = p' + p'' = k'v + k''v^2,$$

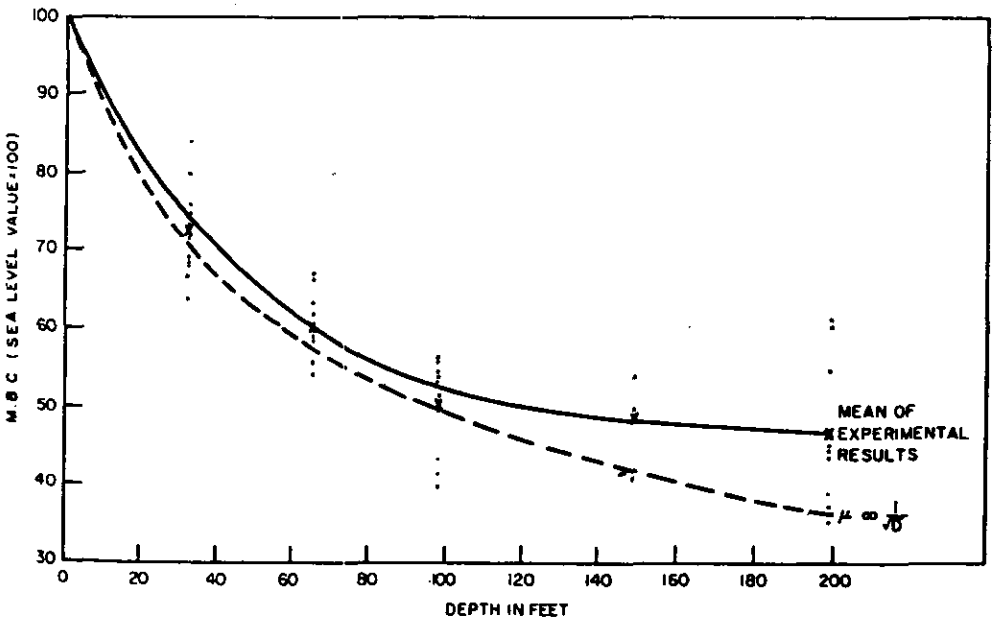


Fig. 11. Maximum breathing capacity (MBC) at various theoretical depths according to experimental data and the formula: MBC = $1/\sqrt{\delta}$ (from Miles, 1957).

*Only Behnke and coworkers have obtained values proportional to $1/\sqrt{\delta}$. However, it must be taken into consideration that their experiments were not carried out on a man, but on a breathing machine at 15 inspirations and expirations/min with an output of 64 liters/min. Furthermore, the machine was built with pipes of various diameters (the smallest was 19 millimeters), so that it must be assumed that the movement of fluid in them was entirely turbulent.

where the pressure drops that can be charged to the turbulence fraction are represented as a function of velocity squared (*Reynolds, Saph-Schoder,* Fritzsche).

The coefficients of this equation, applied to human airways, were studied in detail by Rohrer in his fundamental monograph. We will recall only the essential parts.

In a laminar regime, resistance is (Poiseuille's formula):

$$p' = \frac{8\ L\ \nu\ \eta}{981\ s}\ \text{cm}\ H_2O \qquad \text{(IV,A,2)}$$

where:

η = viscosity of the fluid in absolute units
s = cross section
L = length
v = velocity

If we refer to gas flow (Q) in liters per second rather than to velocity, because $v = Q/s$, we have:

$$p' = k'\ \frac{L}{s^2}\ Q,$$

$$k' = \frac{10^7 \times 8 \times \pi \times \eta}{981}$$

therefore k' is 47.986 for air and for the nitrogen-oxygen mixtures, and 53.03 for the helium mixture (with 5 percent of oxygen). Given:

$$w' = \frac{L}{s^2}$$

we have:

$$p' = k'w'Q,$$

an expression that represents a pressure drop due to viscous resistance caused by laminar flow.

We consider now the various resistances due to turbulence. The resistance resulting from change in size of the passage from one tube to another will be, according to the Carnot-Borda formula:

$$p = \frac{\delta}{2\ g}(v' - v'')^2,$$

where δ represents gas density in kg/m3 (for air at 37°C = 1.117 x H kc/m3, and for the helium mixture = 0.179 x H kg/m3) and g is the acceleration of gravity (9.81 m/sec).

According to Torricelli, resistances due to expulsion of gas externally or to its penetration into the breathing pathways will be:

$$p = \frac{\delta}{2g} v^2.$$

Finally, according to Weissbach, the resistance due to change in the direction of the ducts will be represented by:

$$p = \xi \frac{\delta}{2g} v^2,$$

where ξ is a coefficient whose proportion depends on the various angles. This was accurately analyzed by Rohrer in relation to anatomic conditions of the human respiratory apparatus and was found to be similar to 0.1.

Now, if we indicate the value of the cross section of the trachea by s', and we use s_n to denote the sum of cross sections of the other airways (both in square centimeters), giving to s'/s_n the value of a_n, according to Rohrer (1915), pressure drop due to total turbulence will be:

$$p'' = \frac{\delta}{2g} \times v^2 \times \xi \times \Sigma (a^2_n). \qquad \text{(IV,A,3)}$$

If we next assume:

$$k'' = \xi \frac{H}{2g} \times \frac{100}{s^2}$$

and:

$$w'' = a^2 + \Sigma (a_{n-1} - a_n)^2 + \xi \times \Sigma (a^2_n);$$

the whole pressure drop, then, will be (Rohrer):

$$p = p' + p'' = k'w'Q + \delta k''w''Q^2. \qquad \text{(IV,A,4)}$$

For $s' = 3.393$ square centimeters, we have:

$$k'' = \frac{0.1 \times H \times 100}{2 \times 9.81 \times 3.393^2} - 0.044275\ H.$$

Then, for air $\delta k'' = 0.049451 \times H$, and for the helium mixture (with 5 percent oxygen): $\delta k'' = 0.007925 \times H$.

Rohrer (1915) calculated the values of w' and w'' in the various ducts of the airways by accurate anatomical analysis of many corpse lungs. If we subtract from the totals obtained by Rohrer the amount due to nasal passages (scuba diver breathes entirely through the mouth), we have:

$$w' = 0.0077$$
$$w'' = 13.86.$$

The experimental measurement of mouth-alveolar gradients, carried out by Otis and Proctor by the intermittent interruption of flow method in numerous

human subjects, yielded the following results for air: $k'wi = 3.4$; $\delta k''w'' = 1.5$. Otis and Bembower obtained the same corresponding values during respiration of air at a simulated altitude of 36,000 feet and of helium at ground level. They naturally took into account in both cases the different densities and viscosities of the gases used. From experimental data by these authors, we have:

$$K' = k'w' = 0.0256196 \times 10^7 \eta w'$$

where:

$$w' = w'_i + w'_a = 0.0077 + 0.065219 = 0.072919,$$

if w'_i is Rohrer's coefficient and w'_a the additional increment.

Analogously:

$$K'' = k''w'' = 0.044275 \times H \times w''$$

where:

$$w'' = w''_i + w''_a = 13.86 + 16.473 - 30.333,$$

if w''_i is Rohrer's coefficient and w''_a the additional increment.

It is clear that the additional increments, having no anatomic justification, must be ascribed to particular conditions of the experiment and, therefore, to the breathing apparatus used for the control of gas volumes.

By employing the additional increments, the solution of Eq. (IV,A,4) results in an increase of about 4 cm H_2O/liter/sec (which Mead considered the average value of resistances added to man by good underwater breathing apparatus), we will maintain the additional increments for all of our calculations on underwater breathing with scuba.* In fact, this measure is undoubtedly valid for the closed-circuit scuba, and probably for the expiratory phase of open-circuit scuba. In the latest models of open-circuit scuba, inspiration is aided by special (assisted) mechanisms so that the additional inspiratory resistance is only 1.5 cm H_2O/liter/sec (Giullerme and Rivoire).

Equation (IV,A,4) can therefore be written:

$$p = k' (w'_i + w'_a) \times Q + k'' (w''_i + w''_a) \times Q^2 \text{ cm } H_2O,$$

bearing in mind that in order to obtain values in mm Hg, as is required in Fig. 10, we must multiply the terms by the correction factor (0.7355). It must be borne in mind, however, that w'_i and w''_a must be corrected in relation to the

*According to the tests of Silverman and coworkers, carried out with various amounts of flow, the total resistances (respiratory tree plus breathing apparatus) should never exceed 12 cm H_2O. However, Cooper (1960) observes that expiratory resistances are much more important, and that the resistances added to inspiration may even reach 6 cm H_2O, but expiratory resistances must be necessarily maintained below 4.1 cm H_2O. This is why Lanphier announced plans for scuba with aided expiration.

actual state of chest expansion. Cooper (1961) has observed that in considerable increases of chest volume the experimental measure of p remains markedly below its theoretical values, calculated on the basis of Eq. (IV,A,4). In effect, when new ducts are opened to the flow* or, in any case, when the cross section of the ducts is increased, the velocity of flow decreases and, as a consequence, the magnitude of w also decreases (Eqs. (IV,A,2-4)). Cooper tried to state his case mathematically.

We will try to apply these concepts to changes in vital capacity observed at high pressure. Rohrer (1915) observed that in average and maximum conditions of pulmonary expansion, the cross sections of the bronchial ducts increased by 1.3 to 1.4 times, whereas the velocity of flow in them was reduced to about three fourths of their theoretical value. An exact calculation may be based on Fig. 10.

Thus, in consideration of what has been said concerning VC under hyperpressure, we have:

$$w'_i = \frac{L\sqrt[3]{0.77\ c}}{s^2\sqrt[3]{(0.77\ c)^4}} = \frac{1}{129.87\ (1 + 0.77\ c)}$$

$$w''_i = \frac{s'^2}{s_n\ (1 + \sqrt{0.77\ c})} = \frac{11.5}{0.83\ (1 + \sqrt{0.77\ c})}$$

Table IX gives the coefficients w' and w'' at various environmental pressures as a function of variations of VC (Table VIII); Table IX also gives K' and K''. Thus, it is possible to calculate the degree of mouth-alveolar gradient for each given volume of flow at various environmental pressures.

TABLE IX
Coefficients of Mouth-Alveolar Gradients at Various Depths

Depth		$w' = w'_i + w'_a$	K' = k'w'		$w'' = w''_i + w''_a$	K'' = k''w''
Meters	atm		Air	Mixture of Helium		
0	1	0.07292	3.5	3.74	30.333	1.343
10	2	0.06873	3.298	3.522	27.983	2.478
20	3	0.06745	3.237	3.456	26.124	3.471
30	4	0.06683	3.207	3.424	25.953	4.596
40	5	0.06645	3.189	3.405	25.858	5.725
50	6	0.06623	3.178	3.394	25.824	6.858
60	7	0.06605	3.169	3.384	25.770	7.987
70	8	0.06593	3.164	3.378	25.752	9.121
80	9	0.06583	3.159	3.373	25.747	10.259
90	10	0.06575	3.155	3.369	25.742	11.397
100	11	0.06568	3.152	3.365	25.738	12.534

*In insufflations of isolated dog lungs, Marshall observed that the diameter of the ducts increased 60 percent when their length increased 40 percent.

Theoretically, the maximum respiratory resistance to breathing that a subject could overcome during an entire respiratory cycle (Fig. 10) would be 80 mm Hg. In practice (Margaria), however, it is very unlikely that a subject could succeed in breathing for a reasonable period of time against pressures greater than 50 mm Hg (68 cm H_2O). Table X (fifth column) shows the amounts of flow (Q) for such a pressure gradient (Q_{50}), both for air and for a mixture of helium, considering that from Eq. (IV,A,4) we have:

$$Q = \frac{\sqrt{K'^2 + 4\,\delta\,K''\,p} - K'}{2\,\delta\,K''}, \qquad \text{(IV,A,4a)}$$

recalling that p is expressed in cm H_2O.

Table X also shows (last two columns) values of the percentage reduction in pulmonary ventilation ($V = 1/2 \times Q \times 60$), corresponding to an output of Q_{50}, on the hypothesis that the gas flow that passes through the ducts is steady.

These extrapolated data are in agreement with the averages of experimental data of MBC obtained by numerous authors (Miles; Seusing et al.; Zannini et al.; Wood).

The most important data in Table X shows that the helium mixture with 5 percent oxygen permits a normal MBC, even at a depth of 70 meters, and the reduction of maximum ventilation with the same mixture at 100 meters is still within tolerable limits.

Contrary to what might be supposed, MBC is therefore in close relation with the value of the inverse of pressure drop due to respiratory resistance. This will be even clearer when, in reference to respiratory work, it will be noted that at high rates of ventilation the passive resistance during the expiratory phase exceeds the elastic potential stored during inspiration, and expiration is performed with active participation of expiratory muscles. Instead, during

TABLE X
Maximum Tolerable Respiratory Flow
at Various Environmental Pressures

Depth		$\delta K''$		Q_{50} (liters/sec)		Percent of normal MBC	
Meters	atm	Air	Mixture of Helium	Air	Mixture of Helium	Air	Mixture of Helium
0	1	1.5	0.215	5.667	11.100	—	+95.87
10	2	2.768	0.396	4.400	9.432	-22.36	+66.44
20	3	3.876	0.554	3.794	8.393	-33.05	+48.10
30	4	5.134	0.734	3.342	7.602	-41.03	+34.14
40	5	6.394	0.914	3.026	6.991	-46.60	+23.36
50	6	7.662	1.095	2.780	6.488	-50.94	+14.49
60	7	8.921	1.276	2.589	6.093	-54.31	+ 7.52
70	8	10.188	1.457	2.433	5.765	-57.07	+ 1.73
80	9	11.459	1.639	2.296	5.497	-59.48	+ 3.00
90	10	12.730	1.820	2.190	5.258	-61.36	+ 7.22
100	11	14.000	2.002	2.094	5.045	-63.05	+10.97

execution of the forced expiratory volume (in 1 second) (FEVS), a certain amount of expiratory work is carried out at the expense of potential energy accumulated during inspiration. This is why (shown in experimental data by Zannini and coworkers and by Wood) the reduction of FEVS cannot be superimposed on that of MBC.

When we consider the entire respiratory cycle, the total mouth-alveolar pressure gradient required may be expressed by:

$$dp = KV + K' \frac{dV}{dt} + \delta K'' \frac{dV^2}{dt} ,$$

where the term KV refers to elastic resistances and the value of K is 8.5 (Otis et al., 1950), and K' and K" are the usual constants.

Respiratory work will be expressed by the product dp x dV. However, because the velocity of respiratory flow (and, therefore, the dV/dt ratio) varies during the course of the cycle, it is necessary to integrate the force over the whole volume change. Proctor and Hardy have assumed that the breathing follows a sine curve, making it possible to formulate the hypothesis (Otis et al., 1950):

$$Q = dV/dt = a \times \text{sine } 2\pi \times f \times t;$$

where:

- a = instantaneous maximal flow = π f V_t
- f = frequency of breaths per second
- t = time in seconds
- v_t = tidal volume in liters

Because the total rate of respiratory work can be expressed only by the inspiratory work—expiration (at least for low rates of ventilation) is entirely passive and is carried out at the expense of elastic potential energy stored during inspiration—the work performed per respiratory cycle may be expressed by:

$$RW = \int_o^{\frac{1}{2}f} dp \times dV = \int_o^{\frac{1}{2}f} dp \times a \times \text{sine } 2\pi \, f \, t \times dt .$$

In addition, because

$$dp = \frac{Ka}{2\pi f}(1 - \cos 2\pi \, f \, t) + K' \, a \text{ sine } 2\pi \, f \, t + \delta \, K''(a \text{ sine } 2\pi \, f \, t)^2$$

the work of half a respiratory cycle per second may be expressed by:

$$RW = \frac{K \, a^2}{2\pi^2 f^2} + \frac{K' \, a^2}{4 \, f} + \frac{2 \, \delta \, K'' \, a^3}{3\pi \, f} \text{ kg-m/cm/sec},$$

and because $a/\pi \, f = V_t$, if f refers to 60 seconds:

$$RW = \frac{1}{2} K \, V_t^2 + \frac{K' \pi^2 \, f \, V_t^2}{4 \times 60} + \frac{2 \, K'' \pi^2 \, f^2 \, V_t^3}{3 \times 3,600} \text{ kg-m/cm/sec};$$

and for 1 minute (Otis et al., 1950):

$$RW = 4.25\,K\,V_t^2 + 0.0411\,K'\,\dot{V}^2 + 0.00183\,\delta\,K''\,\dot{V}^3 \text{ kg-m/cm/min} \qquad \text{(IV,A,5)}$$

where $\dot{V}$, by custom, indicates pulmonary ventilation in liters per minute. Naturally, we must multiply all the members of the second term by 10^{-2} to obtain the values in kpm.

In Eq. (IV,A,5), the first member of the second term expresses elastic work; the second, viscous; and the third, work due to the turbulence fraction of the air flow.

When because of the increase in gas density or for very high rates of ventilation, the sum of the second and third members of the second term of Eq. (IV, A,5) is greater than the magnitude of the elastic work, then (Otis et al., 1950) expiration becomes partially active and, therefore, the total work will be double the passive resistances of half a cycle. It follows that Eq. (IV,A,5) will become:

$$RW = 8.22\,K'\,\dot{V}^2 \times 10^{-4} + 0.366 \times \delta\,K'' \times \dot{V}^3 \times 10^{-4} \text{ kpg/min.} \qquad \text{(IV,A,6)}$$

It is worth noting that in Eqs. (IV,A,5 and 6) V_t may be substituted by $V_a + V_d$ (and, therefore, $V = V_a + V_d$) because the tidal volume consists of the sum of the alveolar volume (V_a) and of the functional dead space (V_d). In this way, it is possible to calculate the maximum respiratory efficiency in relationship to frequency (Fenn). Milic-Emili and coworkers have observed that for every rate of ventilation and of oxygen consumption there exists an optimum frequency in which respiratory work is minimal, and that the organism tends spontaneously toward this regulation.

The reason for this is evident from Fig. 12, where it is observed that for the same alveolar ventilation ($\dot{V}_a$ = 6 liters/min) the viscous and turbulent work increased rather linearly with the frequency increase and (up to a certain point) the elastic work decreased. It seems clear, then, that in hyperbaric conditions, when the turbulent work increases, even though the increased density of gas is the primary cause, less work may be required by a decrease in frequency.* In an earlier study, Ciulla and coworkers were able to note that this is observed in subjects already conditioned to high pressure, whereas the tendency to self-regulation is lacking in untrained subjects,† Therefore, in the study of the professional's hyperbaric respiratory work, this training must be taken into account.

An experiment was conducted at sea to study the behavior of breathing rate and tidal volume at depths of 0, 20, 40, 60, 80, and 100 meters. Air and a mixture of helium containing various percentages of oxygen according to the depth were used (20 percent for 0 to 20 meters, 10 percent for 40 and 60 meters, and 5 percent for 80 and 100 meters). To reduce the differences in oxygen

*In the last century, Marey observed that the increase in respiratory resistances is accompanied by a decrease in frequency and an increase in amplitude of breaths. This observation was confirmed by later authors (Moravitz and Siebeck; Davies et al.; Hewlett et al.; Killick; DiGiorgio and Giulio).

†In 1936, Fegler already had observed that the increase in respiratory resistances induced a decrease in respiration in trained subjects, but an increase in others.

consumption from one depth to another, the subjects—who swam at a speed of 1 knot—did not use a thermal suit. In addition, areas were selected where the temperature of the water was 14°C at the depth of each experiment. The stay at the deeper depths was limited to 3 minutes (to avoid lengthy decompression periods for subjects without thermal protection). The stay at shallower depths was maintained from 5 to 15 minutes so as to precisely measure the gas inhaled. This was calculated on the basis of the pressure difference of the content of the cylinders from which the subjects had breathed on open circuit only for the time prescribed at the depths. Pulmonary ventilation was calculated by dividing the total gas inhaled (and corrected for BTPS) by the time.

The breathing rate was directly controlled by emission of discharge gas, and the tidal volume was obtained by dividing the ventilation by the breathing rate. Finally, respiratory work was calculated with the use of Eqs. (IV,A,5 and 6).

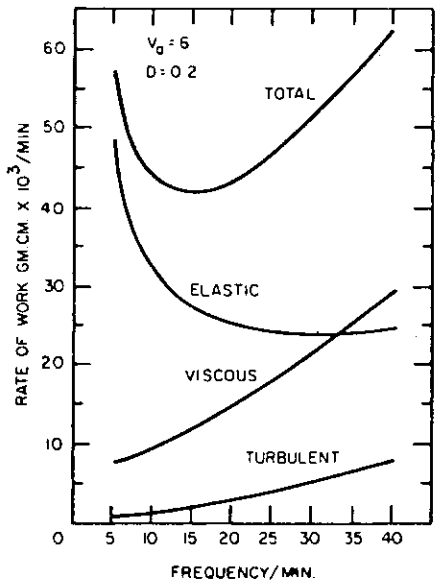
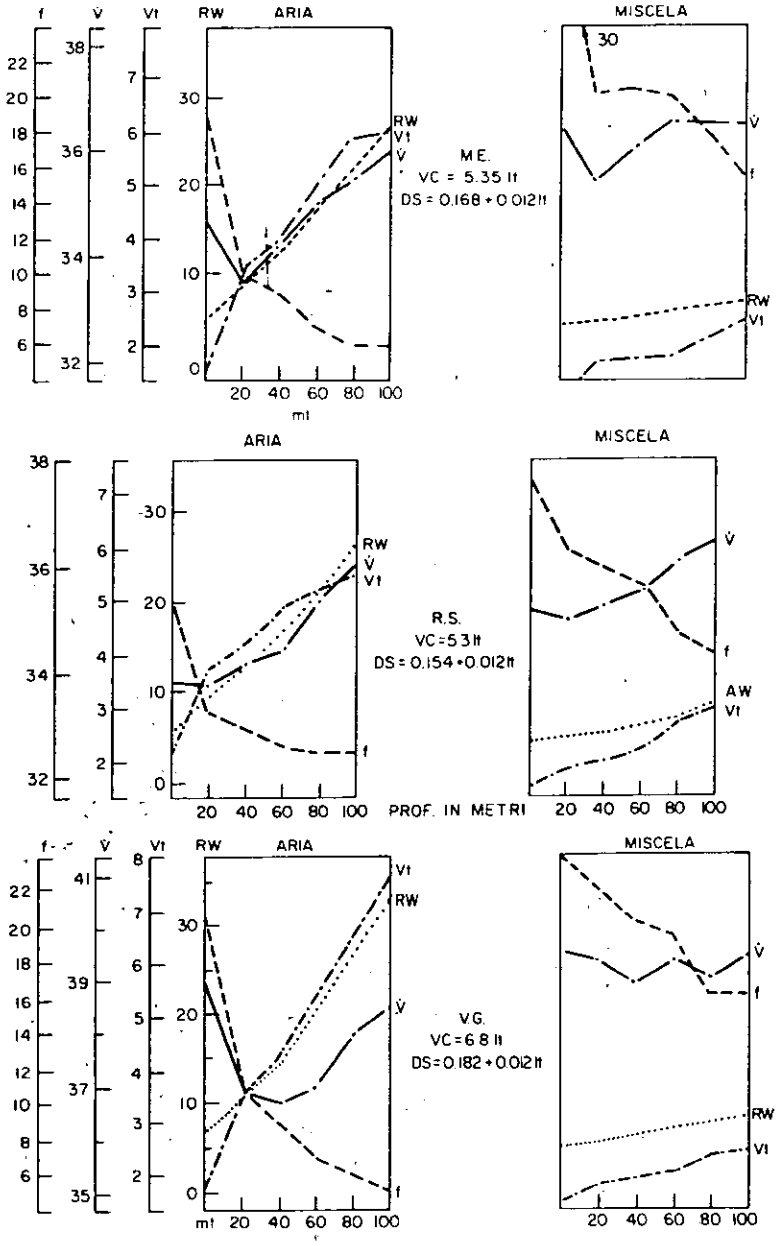


Fig. 12. The three fractions and the total respiratory work at various breathing rates for a subject breathing with V_a of 0.6 liter and with DS of 200 milliliters (Otis et al., 1950).

The results for the three subjects are given in Fig. 13. Immediately apparent is the notable and progressive reduction in the rate breathing air with an increase in environmental pressure. For depths of 30 to 40 meters, this produces a clear decrease in pulmonary ventilation, which is in agreement with data compiled by the Cooperative Underwater Swimmers Project and with earlier research (Ciulla et al.). However, as the depth is increased, there is no further increase in tidal volume due to high alveolar ventilation (much greater than that used by us in experiments in hyperbaric chambers). It was noted that there was a rise in rates of pulmonary ventilation due to greater demands (increase in pulmonary loss of heat). This phenomenon is less evident breathing a helium mixture, which involves only a moderate amount of respiratory work. When breathing air, however, the respiratory work increase, between 0 and 100 meters, is on the order of one to five. Thus, air ventilation for action subjects without thermal protection at a depth of 100 meters was extremely laborious, and was considered as the subjects' physiological limit and, in any case, tolerable for only a few minutes.

Another important fact derived during air breathing observations was that the tidal volume increased beyond the VC at ground level. This constitutes an indirect confirmation—and is made possible by—of what has been said at the beginning of this chapter on the behavior of VC at high pressure. To better illustrate this point, Fig. 14 was constructed so that the V_t/VC ratio was placed in relation to depth. It can be clearly observed how, during respiration of air at the maximum depth, the V_t/VC ratio shows, on the average, values close to those theoretically calculated in Table VIII. This means that the amplitude of breaths has reached its maximum (or almost), that is, that of the actual VC. In practice, the value of



KEY:

$\dot{V}$ indicates pulmonary ventilation in liters/min

V_t indicates tidal volume in liters

f indicates breathing rate in breath/min

RW indicates respiratory work in kpm/min breathing air and a mixture of helium and oxygen at various depths.

Fig. 13. Results of experiments on the behavior of breathing rate and tidal volume. (a) Subject M.E.: VC = 5.35 liters, DS = 0.168 + 0.012 liter; (b) subject R.S.: VC = 5.3 liters, DS = 0.154 + 0.012 liter; (c) subject V.G.: VC = 6.8 liters, DS = 0.182 + 0.012 liter.

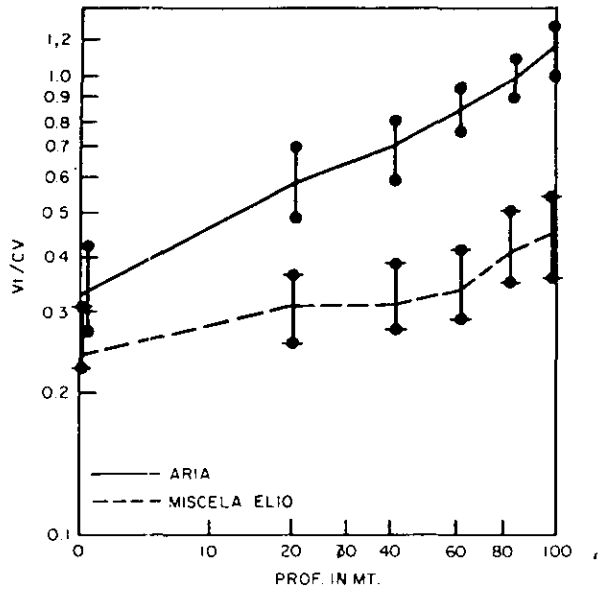


Fig. 14. Average of V_t/VC relationship on three subjects at various depths breathing air and a helium-oxygen mixture, plotted on a semilogarithmic scale.

the quotient increases an average of four times with air, whereas it increases less than twice with a mixture of helium.

Aside from any other consideration, these experimental results indicate that it is unadvisable to use air as a breathing mixture for deep dives. However, to clarify this point, Table XI was constructed. Table XI shows, on the basis of Eqs. (IV,A,5 and 6), the respiratory work for ventilation rates commonly required at various depths by subjects wearing thermal protection with neoprene suits, in accordance with references in Ch. III ($\dot{V}a$ = 24 and 30 liters/min). Thus, in Table XII, the same calculation was used for a helium mixture. In order to understand the importance of the data tabulated, it is necessary to add some considerations on the incidence of respiratory work in the total energy balance of work.

The purpose of respiration is to assume oxygen and eliminate carbon dioxide. Thus, we may speak of an energetic equivalent of respiration. As will be seen later, even if a greater partial pressure of oxygen is administered at high pressure, the amount of this gas actually assumed by the blood varies little because the hemoglobin is already almost entirely saturated (96 percent) through normal pressure (150 mm Hg). Thus, we may speak of an energetic respiration equivalent, more or less independent of various oxygen pressures.

According to research by Margaria (1938), for each liter of alveolar air ventilated, there is an equivalent of 0.328 ± 0.00132 kilocalorie corresponding to the elimination of 47 milliliters of CO_2 and to the assumption of 56 milliliters of O_2. However, Margaria has observed that this linear relationship is

TABLE XI

Respiratory Work at Various Depths Breathing Compressed Air With DS of 0.25 Liter

Depth (meters)	Pressure (ata)	4.1125 K'	0.183 δK''	V_a = 24 (liters/min)		V_a = 30 (liters/min)		V_a = 7 (liters/min)	
				Frequency	RW in (kpm/min)	Frequency	RW in (kpm/min)	Frequency	RW in (kpm/min)
0	1	14.39	0.2745	20	3.748	20	5.860	14	0.528
10	2	13.56	0.5065	15	4.306	15	6.982	14	0.542
20	3	13.31	0.7093	12	4.946	12	7.996	14	0.563
30	4	13.19	0.9394	11	5.554	10	9.334	14	0.588
40	5	13.11	1.1701	10	6.196	9	10.602	14	0.603
50	6	13.07	1.4021	9	6.874	8	11.864	13	0.631
60	7	13.03	1.6325	8	7.498	7	13.134	13	0.656
70	8	13.01	1.8644	7	8.100	6	14.234	13	0.681
80	9	12.99	2.0970	6	8.716	6	15.686	12	0.694
90	10	12.97	2.3296	6	9.402	6	17.134	12	0.716
100	11	12.96	2.5620	5.5	10.018	6	18.592	11	0.728

TABLE XII

Respiratory Work at Various Depths Breathing a Mixture of Helium (With 5 Percent Oxygen) With DS of 0.25 Liter

Depth (meters)	Pressure (ata)	4.1125K'	0.183 δK''	Va = 24 (liters/min)		Va = 30 (liters/min)		Va = 35 (liters/min)	
				Frequency	RW in (kpm/min)	Frequency	RW in (kpm/min)	Frequency	RW in (kpm/min)
0	1	15.38	0.0393	25	3.072	25	4.442	25	5.686
10	2	14.48	0.0725	25	3.081	25	4.496	25	5.944
20	3	14.21	0.1014	25	3.162	25	4.709	22	6.271
30	4	14.08	0.1343	20	3.296	20	4.901	20	6.512
40	5	14.00	0.1673	20	3.370	20	5.032	20	6.711
50	6	13.96	0.2004	20	3.448	20	5.169	20	7.034
60	7	13.92	0.2335	20	3.525	20	5.406	18	7.295
70	8	13.89	0.2666	20	3.636	18	5.559	18	7.600
80	9	13.87	0.2999	17	3.769	18	5.764	16	7.929
90	10	13.85	0.3331	17	3.842	16	5.981	16	8.164
100	11	13.84	0.3664	17	3.917	16	6.112	16	8.556

no longer maintained for the higher rates of ventilation when the blood remains in the pulmonary capillaries too briefly for the gases to achieve equilibrium across the alveolar membrane.*

However, it must be considered, as Rossier and Bühlmann have stressed, that with the increase in pulmonary ventilation the production of energetic equivalents increases proportionately, whereas oxygen consumption by the respiratory apparatus increases exponentially. Thus, a critical point may be reached at which every further increase in ventilation results in increased consumption of equivalents greater than the amount produced. This may be understood by a simple calculation.

Fenn demonstrated, by analysis of data provided by Liljestrand on oxygen consumption, that the mechanical efficiency of respiratory muscles is only 5 percent,† whereas that of other skeletal muscles is 23 percent. This is related to the fact that for every kpm of respiratory work there is an energy consumption of 0.002343 x 20 = 0.04686 kilocalorie, which means that the critical point is reached by:

$$RW = \frac{0.328\ \dot{V}a - (M + EBW)}{0.04686}$$

where:

M = extramuscular metabolism
EBW = energy consumption of muscles at work

If we consider M = MB (and this is valid if the mechanical efficiency, BW, is considered equal to 23 percent of EBW), we have:

$$\frac{0.002343\ BW}{0.23} = EBW = 0.328\ \dot{V}a - (MB + 0.04686\ RW) \qquad (IV,A,7)$$

that is:

$$BW = \frac{0.328\ \dot{V}a - (MB + 0.04686\ RW)}{0.0102}\ kpm/min \qquad (IV,A,7a)$$

where BW (bodily work) represents the maximum mechanical work the extrarespiratory muscles can perform for the $\dot{V}a$; and MB is the value of basal metabolism in kcal/min.

*On the other hand, the transfer of carbon dioxide from the blood to the alveoli does not undergo change because the high solubility of this gas permits it to penetrate the alveolar-capillary membrane 20 times the velocity of oxygen.

†In fact, the work conditions of respiratory muscles are as advantageous as those of other skeletal muscles (Fenn.) However, it must be considered that the total energy cost of respiration is not exhausted through mechanical work. In fact, it may be expressed by: $E = e' + e'' + e''' + e''''$; where: e' refers to elastic work (potential chest-pulmonary energy); e'' refers to resisting work (viscous and turbulent); e''' to loss of energy due to the passage of gas from pressure p_a to p_o isothermically: $e''' = n \times RT \times \ln (P_a/P_o)$; and e'''' refers to losses due to kinetic energy of gases exhaled:

$$e'''' = \int_{V'}^{V''} 1/2 v^2 d_m.$$

Regarding muscular work (Ch. I, Sec. C)), we have seen that the maximum aerobic bodily work a normal-average subject can perform breathing air at ground level is about 1,800 kpm/min ($_{EBW}$ = 18 kcal/min). Under such conditions, if the dead space (including that of the respirator) is 0.25 liter, with a frequency of 32 breaths/min and $\dot{V}_a$ of 64 liters/min, the $_{RW}$ value ($\dot{V}_a$= 72 liters/min) is 35.28 kpm/min, with an expense of 1.65 kcal/min. On the other hand, the energetic equivalent of ventilation will be: 0.328 x 64 = 20.9 kcal/min, which will be expended through basal metabolism (1.218 kcal/min), ventilation work (1.65 kcal/min), and bodily work due to the subject's activity (18 kcal/min). Each further increase in energy requirement demands from the respiratory muscles a consistent increase in energy consumption. This cycle creates a situation in which, under work conditions, the 64 liters/min can be considered the critical point of alveolar ventilation of air at ground level beyond which dyspnea is structured (Rossier and Bühlmann).

Although some authors maintain that during the $_{MBC}$ test, the respiratory muscles are able to carry out a high order of mechanical work (80 kpm/min, according to McIlroy and coworkers, and even as high as 250 kpm/min according to Comroe), it must be carefully considered that under work conditions the matter is quite different because of fatigue. As was seen in Fig. 3, work amounting to 250 cal/kg/min (equivalent to 18 kcal/min, in a subject weighing 72.5 kilograms) is carried out mostly in anaerobiosis and leads to exhaustion in 6 minutes because of the need to use energetic equivalents of ventilation to restore the oxygen debt contracted. For work of longer duration, the need for continuous aerobic exchange insured by an easy respiration must be carefully considered.

The practical limit of admissible respiratory work may be established by the ventilation rate that can be obtained without the intervention of auxiliary respiratory muscles. Campbell's electromyographic investigations show that in an average number of subjects at ground level this corresponds to breathing air to a ventilation of 50 liters/min which, according to Eq. (IV,A,6), is equivalent to respiratory work of 14 kpm/min.

Table XIII shows values of $\dot{V}_a$ and of $_{BW}$ for this degree of $_{RW}$ breathing air and a helium mixture at various depths.

The most important point to emerge from Table XIII is the observation that respiration of a helium mixture at depths between 60 and 100 meters permits an availability of energetic equivalents and maximum work performance by the diver on the order of those obtainable at ground level breathing air. Therefore, it can be unquestionably concluded that, at least from the point of view of ventilation mechanics, the helium mixture must be considered the physiological breathing mixture for underwater work. On the other hand, the notable reduction (about 42 percent observed in work potential at greater depths breathing compressed air makes it unadvisable to use air as a respiratory mixture for underwater work beyond a depth of 50 meters when the energetic equivalents required by thermogenesis cannot be supplied by a sufficient rate of ventilation. However, it must be borne in mind that these conclusions refer only to a high level of demand and cannot be extended to cases of lesser physical activity and thermogenetic requirements. Nor, therefore, can they be applied to subjects at rest in hyperbaric chambers. In fact, as is observed in the last column of Table XI, for a $\dot{V}_a$ of 7 liters/min, which is more than sufficient for subjects at rest at comfortable temperatures, such as in a dry hyperbaric chamber (Albano and

TABLE XIII

Alveolar Ventilation, Energy Availability, Working Efficiency, Instantaneous Maximum Gas Flow, and Relative Head Gradients for RW of 14 kpm/min and With DS of 0.25 Liter

Depth (meters)	Pressure (ata)	V_a (liters/min)		Available Energetic Equivalents (kcal/min)		Maximum RW Permissible (kpm/min)		Maximum Instantaneous Gas Flow (liters/sec)		Heat Gradient (mm/Hg)	
		Air	Helium Mixture	Air	Helium Mixture	Air	Helium Mixture	Air	Helium Mixture	Air	Helium Mixture
0	1	43.75	55.50	14.35	18.20	1.250	1.630	2.62	3.30	9.63	9.60
10	2	39.25	54.00	12.87	17.71	1.100	1.580	2.33	3.19	10.39	9.19
20	3	36.00	52.35	11.81	17.17	1.000	1.530	2.12	3.09	11.09	9.11
30	4	34.75	50.70	11.40	16.63	950	1.475	1.99	2.99	12.21	9.14
40	5	33.00	49.05	10.82	16.09	900	1.420	1.86	2.89	13.03	9.18
50	6	32.00	47.50	10.49	15.58	860	1.370	1.78	2.80	14.19	9.24
60	7	30.75	46.05	10.08	15.10	820	1.320	1.70	2.71	15.11	9.29
70	8	29.75	45.20	9.76	14.82	790	1.295	1.64	2.63	16.11	9.35
80	9	29.00	44.15	9.51	14.48	780	1.260	1.62	2.58	17.42	9.51
90	10	28.10	43.30	9.21	14.20	735	1.240	1.60	2.53	18.60	9.65
100	11	27.20	42.75	8.92	14.02	705	1.215	1.58	2.49	19.20	9.83

Ciulla; Ciulla et al.), the amount of respiratory work is negligible even at higher environmental pressures. Therefore, there seems to be no justification for Bühlmann's theory of alveolar hypoventilation and carbon dioxide retention caused by respiratory overexertion in subjects at rest in compressed air (Albano, 1962).*

A factor to be considered has to do with the gradients that result at high environmental pressure in relation to alveolar structure to which we referred in comments on the volume-pressure diagram (Fig. 10).

With $\bar{Q}$ representing the amount of gas flow passing through the airways every second in both directions, it is clear that on the average:

$$\bar{Q} = 2\dot{V}/YP = 2a/\pi; \text{ whence } a = 1.57\ \bar{Q},$$

which means that the maximum instantaneous flow is:

$$a = 52.36 \times 10^{-3}\ \dot{V} \text{ liters/sec.}$$

The last columns of Table XIII include calculations of the values of the mouth-alveolar gradient in relation to heads of gas flow figured on the basis of Eq. (IV,A,4), in mm Hg, as required in Fig. 10. From the results, it is clear that when breathing the helium mixture, the head gradient remains almost constant without exceeding 10 mm Hg, whereas when breathing air it reaches, at the deepest depths, almost double the amount at ground level regardless of the reduction in alveolar ventilation. However, even when breathing air, the mouth alveolar gradient remains within the physiological limit of 40 mm Hg (Fenn) for the ventilation rates considered. In any case, it must be considered that even high values of head gradients have no harmful effect if they continue for a very brief time, such as periods of coughing, when p may even exceed 150 mm Hg (Geigel), or during defecation, when it also reaches very high levels (Fenn).

However, it should not be believed that maintenance of very high respiratory resistances can be maintained for very long periods without any effect on the delicate-broncho-alveolar structures and, above all, on the alveolar-capillary structures. In fact, it is probable that the pulmonary edema picture described in the literature on animals exposed for many days to air-breathing at more than 5 atmospheres (Hill and McLeod; Bohnenkamp) can be ascribed, at least partially, to protracted breathing against very high resistances.

*A frequently used method for evaluating the respiratory efficiency is the measure of the FEVS. Some authors (Zannini and coworkers; Wood) have tested the FEVS at high environmental pressure. In order to understand the meaning of the results obtained, some considerations must be made. According to Fenn's calculations, the maximum mechanical work that respiratory muscles can perform during one entire respiratory cycle is about 10 kpm/min in average subjects. The maximal expiratory work will be equal to about half this value, plus elastic potential energy stored during the preceding inspiration. Then, from Eq. IV,A,5) we have:

$$\frac{1}{4} K' \pi^2 FEVS^2 \times 10^{-2} + \frac{2}{3} \delta K'' \pi^2 FEVS^3 \times 10^{-2} = 5.0 + 4.25 \times VC^2 \times 10^{-2}\ .$$

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ABSTRACT

Bradley, M.E., N.R. Anthonisen, J. Vorosmarti and P.G. Linaweaver.

Respiratory and Cardiac Responses to Exercise in Subjects Breathing Helium-Oxygen Mixtures at Pressures From Sea Level to 19.2 Atmospheres.

In: Lambertsen, C.J., ed. Underwater Physiology. Proceedings of the Fourth Symposium on Underwater Physiology, p. 325-337. New York, Academic Press, 1971.

The results of this study indicate that man breathing He-O_2 mixtures can perform heavy work for sustained periods to depths of 600 FSW without undue physiological stress. Hypoventilation and CO_2 resulting from increased airway resistance were not demonstrated. During performance of heavy work, there was a progressive increase in O_2 consumption with the increase in depth, most likely reflecting the increased work of breathing. A respiratory pattern of increased tidal volume and decreased respiratory frequency was present during both rest and exercise as depth was increased. This change probably represents an adaptive mechanism to minimize the work of breathing dense gas mixtures. (Authors' summary)

Underwater Physiology

PROCEEDINGS OF THE THIRD SYMPOSIUM ON UNDERWATER PHYSIOLOGY SPONSORED BY THE COMMITTEE ON UNDERSEA WARFARE OF THE NATIONAL ACADEMY OF SCIENCES—NATIONAL RESEARCH COUNCIL AND THE OFFICE OF NAVAL RESEARCH, IN WASHINGTON, D. C., 23, 24, and 25 MARCH 1966.

C. J. LAMBERTSEN / Editor

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Baltimore • 1967

30 | R. W. HAMILTON, JR.

Physiological Responses at Rest and in Exercise During Saturation at 20 Atmospheres of He-O_2

This presentation will describe a chamber saturation dive in which two normal subjects were exposed for 48 hours to a pressure equivalent to 650 feet of sea water, or roughly 200 meters, followed by a multiday decompression breathing helium and oxygen. Part of the justification for the experiment was to assess the operational and medical problems of this type of dive; observations on these topics have been reported elsewhere (6, 11). The major physiological purposes were to establish man's ability to do useful work at these depths, to study the responses to exercise in the high-pressure helium-oxygen environment and to determine the effect that living in this environment has on the respiratory response to CO_2.

Methods

The routine of exercise experiments began several days before the dive, continued through the "bottom time" and resumed again after decompression was complete. The usual procedure was for each subject to do one experiment in the morning and another in the afternoon.

An experiment consisted of a series of measurements taken under control or "resting" conditions, followed by a twenty-minute period of exercise, toward the end of which the measurements were repeated. The measurements included respiratory minute volume, end-tidal P_{CO_2}, cardiac rate response, oxygen consumption and carbon dioxide production (3, 4).

The experiment was conducted in a deck decompression chamber, the one described elsewhere (9) and in this volume (Chapter 9) as a component of the first combined deck decompression chamber-submersible chamber

operation. It is just over 5 feet in diameter with a volume of 138 cubic feet, and was refitted for laboratory use.

The chamber atmosphere during the high pressure phase was 94.5% helium and 4% nitrogen, plus 1.5% oxygen; this was equivalent to breathing 35% oxygen at sea level. With this gas mixture, the density was roughly 3.7 times that of sea level air.

During the pre-dive period procedures were devised and practiced that required a minimum of voice communication from the divers to the observers, since severe speech limitations are imposed by helium at 20 atmospheres.

During each experimental run the subject reclined on the bunk, inspiring chamber gas through a low-resistance valve system and mouthpiece, and expiring through a large stopcock. Exercise was performed by using the same device as that used in the Gemini earth-orbiting spacecraft. The subject stretched a rubber bungee cord by extending his feet, the level of exercise being determined by the frequency of stretching. Each pull to full length required 21 foot pounds or 2.9 kilogram-meters of work.

During the experimental periods the second diver served as technician. By manipulating the stopcock he collected samples of expired gas in 30-liter weather balloons over timed intervals. He then forced the contents of each bag through a dry test gas meter located inside the chamber, and recorded the volume.

The layout of the experiment is shown in Figure 113, which shows the configuration for experiments conducted with the chamber pressurized. Gas analyses were all performed outside the chamber on gas samples reduced to atmospheric pressure. End-expiratory gas for carbon dioxide measurement was sampled continuously from the mouthpiece, reduced to atmospheric pressure, and drawn into an infrared carbon dioxide analyser. A breath-by-breath recording was made from which inspired and end-expired CO_2 tensions were calculated. The same CO_2 sampling line was transferred briefly to each bag of expired gas for a measure of mean expired P_{CO_2}.

Oxygen was sampled from the chamber or the expired gas bag through a nylon sampling line by which samples were passed through a drying tube to a paramagnetic oxygen analyser. An excess flow was used to reduce transit time in the sampling lines. The volume of gas removed from each sample was added to the gas meter reading.

For oxygen analysis in the experiments performed at sea level, a small pump was inserted in the sampling line to force the sample through the analyser at the same rate as when the chamber was under pressure. For sea-level CO_2 analysis, the pickup unit was connected directly to the line leading to the mouthpiece, and standards were introduced through the same lines as the experimental samples.

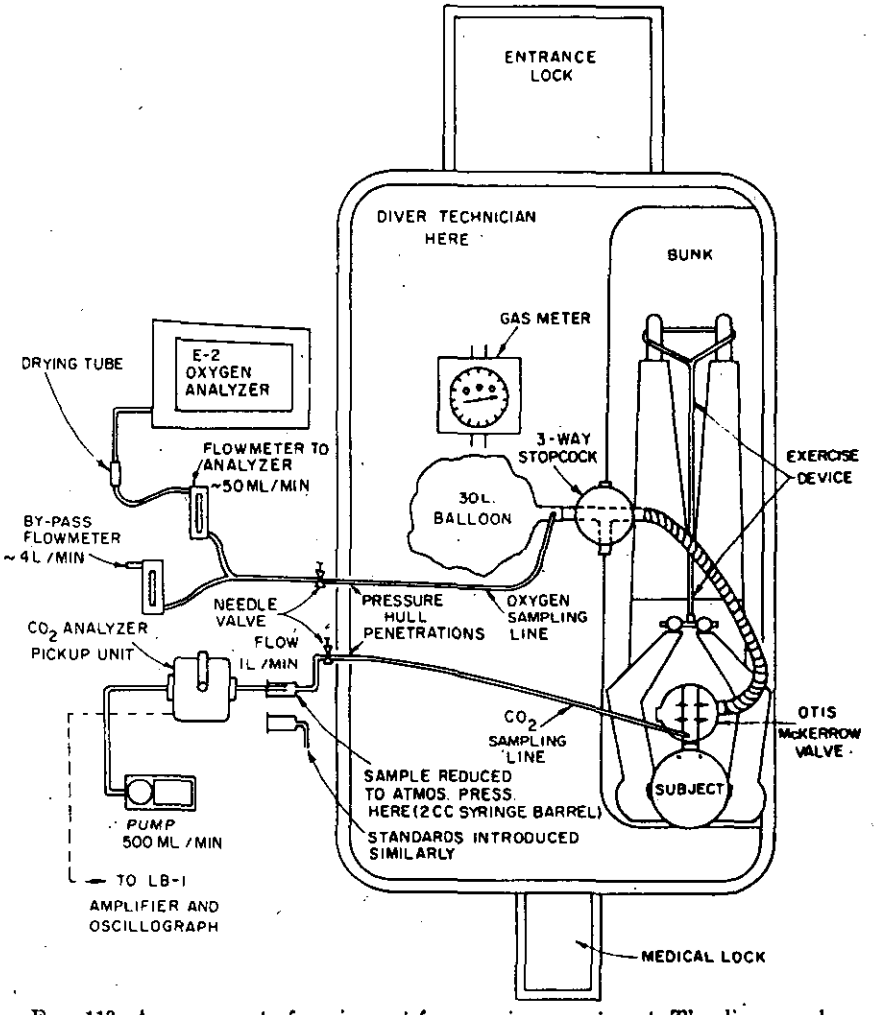

FIG. 113. Arrangement of equipment for exercise experiment. The diagram shows setup for operation with chamber pressurized. The gas sampling lines are shown in the configuration used in experiments with the chamber under pressure. For sea level experiments a pump was added in the oxygen sampling line downstream of the needle valve, and the CO_2 sampling line was connected directly between the pickup unit and the needle valve.

Cardiac rate was monitored continuously throughout each run by means of electrodes attached to the subjects in the morning and left in place all day.

An experiment began by having the subject accommodate to the mouthpiece for at least three minutes and this was followed by two 2-minute sampling periods. He then began to exercise, and after fifteen minutes of

exercise, two more 2-minute collections were made. A single level of exercise was used for each experiment; the maximum rate used during the dive was 174 kilogram-meters per minute, or just over 28 watts. This level resulted in about one liter per minute of oxygen consumption. It would have been desirable to have used additional, higher work levels.

Results and Discussion

In order to assess the physiological significance of experiments such as these, it is necessary to focus on several specific aspects of performance. As a working hypothesis it was assumed that the predominant feature of the high pressure environment would be the increased density of the breathing medium. Other factors that may be important, however, and that must be considered in interpreting our results are: helium as a pharmacological or narcotic agent, the effects of confinement and inactivity, the unusual thermal properties of helium, the high humidity in the chamber, and the slightly increased oxygen tension.

With the thought in mind that effects of gas density on respiration would be the limiting factor, several conditions were considered that might have been affected by the increased work of breathing. Comparisons were made at sea level and at 650 feet of the following parameters: oxygen consumption during exercise, ventilatory response to exercise, change in alveolar carbon dioxide pressure during exercise and the cardiac rate response to exercise.

Since the manner of imposing the amount of work done was somewhat crude, measured oxygen consumption was compared with the intended level of energy output (Fig. 114). It appears that Subject 2 (Christensen) showed about the same oxygen consumption for a given level of exercise at sea level and at depth. Subject 1 (Noble), on the other hand, seems to have consumed more oxygen at depth for a given work load than he did at sea level.

It should be noted in Figure 114 that there was no appreciable change in oxygen consumption at rest while the subjects were in the helium atmosphere, as compared to the sea level values.

Figure 115 shows these same data plotted as differences from control values, which was accomplished by transposing all resting values to the origin. To permit a comparison of the average slopes of the two groups of lines, sea level and 650 feet, the average slope of each group was determined by fitting a least squares regression line to the points. One 0 ,0 value was entered into the calculation along with each of the points shown. Using the *t*-test (5, p. 177), the least squares regression lines representing the averages of the two groups were compared and found not statistically different. So although a given level of exercise appears to require slightly

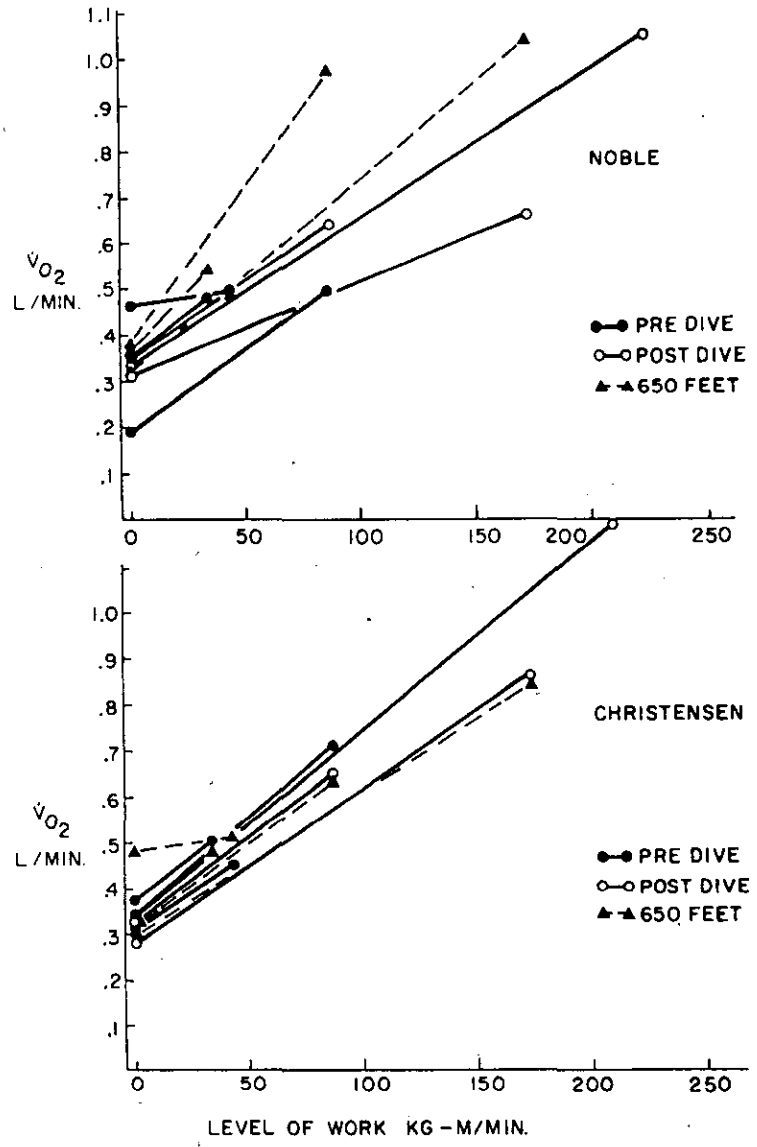

FIG. 114. Oxygen cost of exercise. Oxygen consumption is shown as a function of exercise level.

more oxygen when performed at 20 atmospheres, the difference is not important at the relatively low levels of exercise used in these experiments.

The effect of the dense atmosphere on the ventilatory response to exercise was considered. Figure 116 shows the increase in respiratory minute

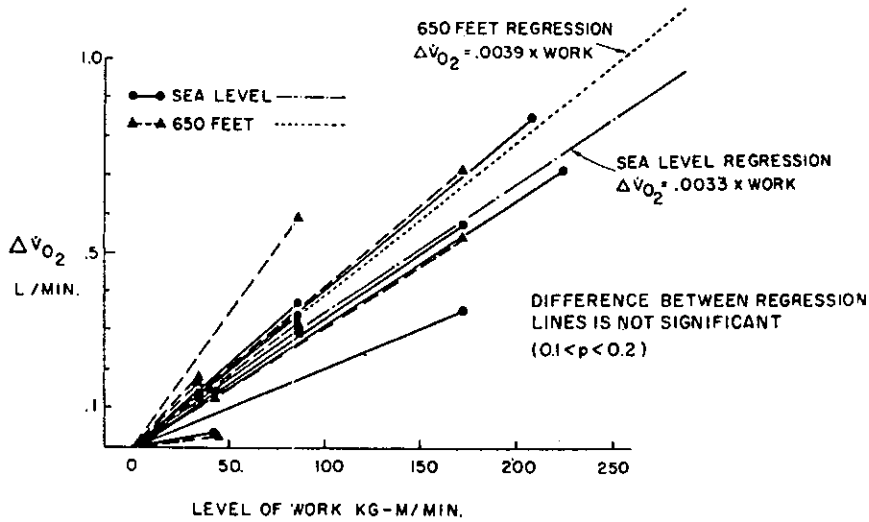

FIG. 115. Oxygen cost of exercise. Composite graph showing increase in oxygen consumption as a function of exercise; data from both subjects. Regression lines were calculated to represent the average slope of each group of points (sea level and 650 feet) using the method of least squares. One "0, 0" point was entered in the calculation for each point shown.

volume as a function of increased oxygen consumption for the same experiments as above. The level of exercise is expressed as oxygen consumption since the oxygen consumption more nearly expresses the actual amount of work performed by the subject than does the number of times he pulled the Gemini exerciser. According to the average values, represented by the least squares regression lines, the ventilatory response to exercise is reduced at depth by 38 % and this reduction is statistically significant. This reduction in ventilation during exercise results in a slight accumulation of CO_2. Figure 117 shows resting alveolar P_{CO_2} values on the left end of each line and values measured after 15 minutes of exercise on the right. (The end-tidal P_{CO_2} values were corrected with an empirically determined factor that corrects for the washout of dead space as a function of tidal volume. It is therefore justified to refer to these P_{CO_2} values as closely approximating "alveolar" (7)). Considerable variation was found, even in the points determined at rest. A significant point is that the resting CO_2 values at 650 feet were not very different from those determined at sea level. The post-dive measurements are indicative of mild hyperventilation; more will be said about the post-dive conditions below.

For comparison all the lines were pooled together and plotted as differences (Figure 118). The dotted lines show that there was a consistent

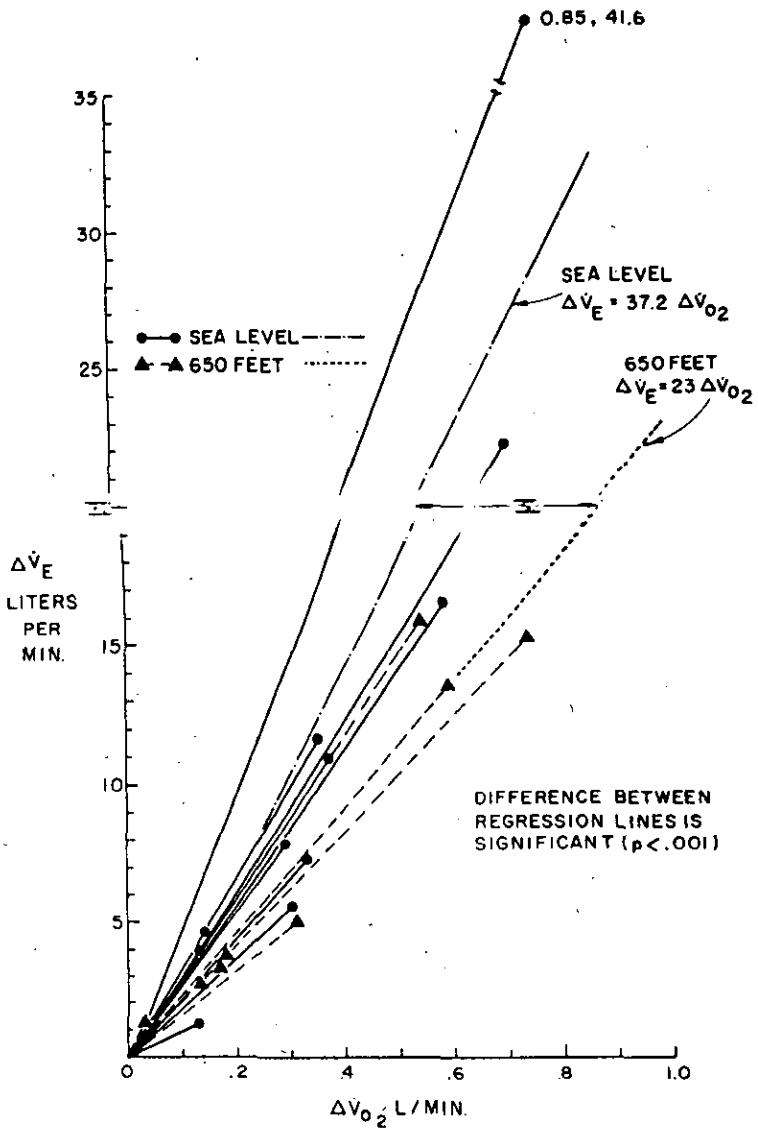

FIG. 116. Increase in ventilation with exercise; data from both subjects. In this and subsequent graphs the level of exercise is represented by oxygen consumption. Regression lines calculated as in Figure 115. The 0.32 value represents the extra oxygen consumed at depth when ventilating at 20 liters/min., but represents more than just the extra work of breathing.

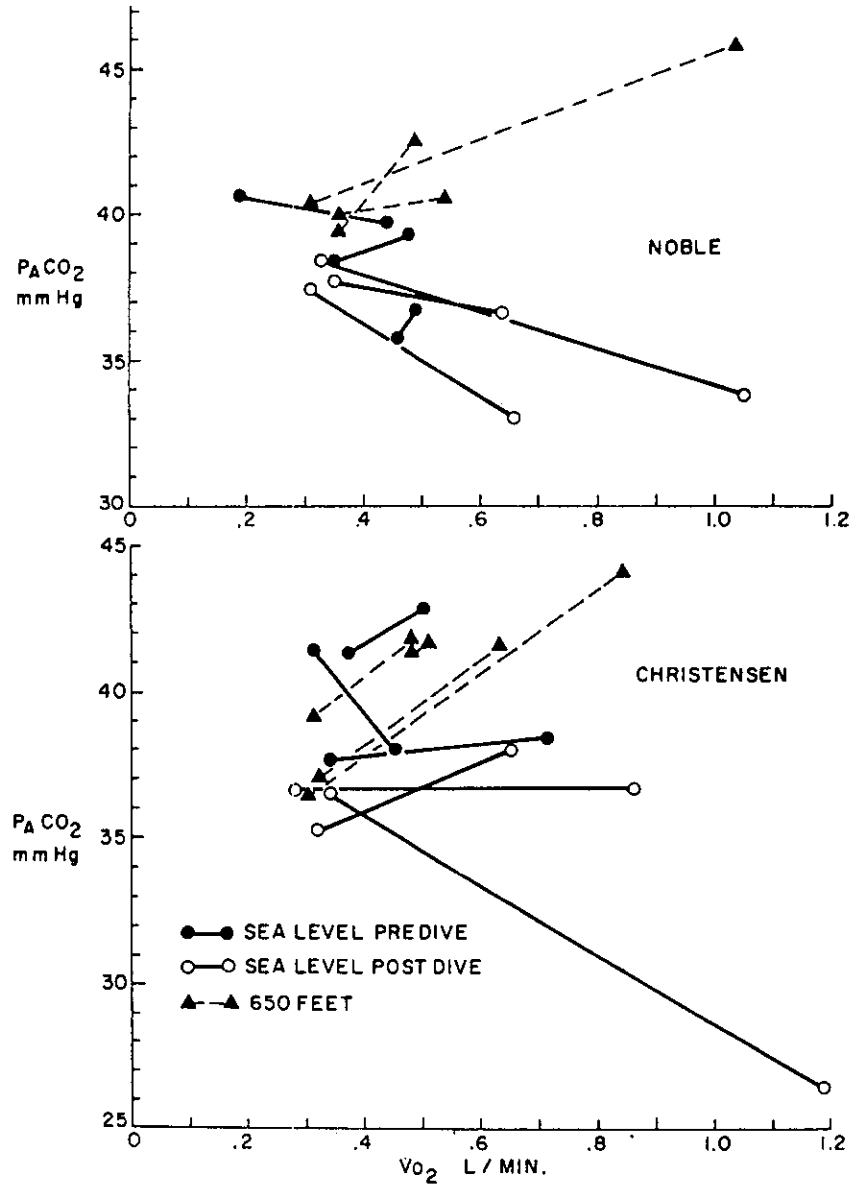

FIG. 117. Effect of exercise on alveolar CO_2. Each line represents a single experiment, with the point on the left end determined at rest and the one on the right after 15 minutes of exercise.

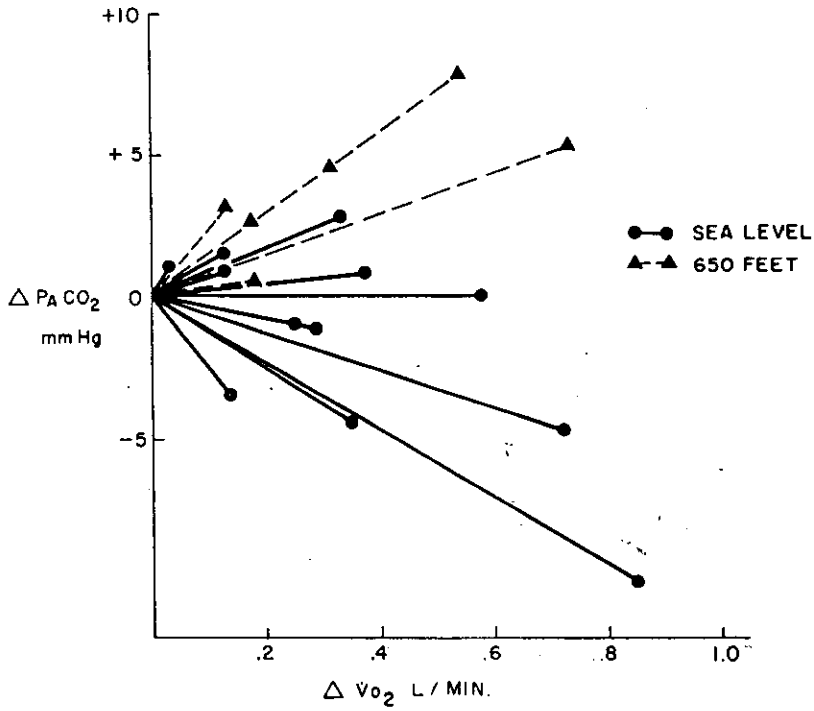

FIG. 118. CO_2 buildup as a result of exercise. Same values (both subjects) as shown in Figure 117, redrawn so as to represent changes from a single starting point. The slight buildup of CO_2 during exercise at 650 feet is evident in all experiments.

tendency for alveolar P_{CO_2} to increase with exercise at 650 feet, while the sea level experiments show the expected slight decrease or no change. This slight rise in P_{CO_2} agrees with some of Lanphier's earlier data, in the cases where gas density and exercise level are comparable (8).

Resting and exercising heart rates are shown in Figure 119. Two things stand out in this figure. One is a tendency for resting heart rates to fall into distinct categories according to the experimental conditions. The other is the occurrence of strikingly parallel responses under all three conditions. The parallel response suggests that there is no special cardiopulmonary stress as a result of moderate exercise at 650 feet.

The resting heart rate values show two features which deserve comment. First, the post-dive rates are unusually high. The days following the long decompression, when the post-dive experiments were carried out, were typical, hot, humid, oppressive August days. The stress of heat and humidity undoubtedly affected the subjects. This, plus the possible effect of six days of physical deconditioning, probably explains the elevated heart rates

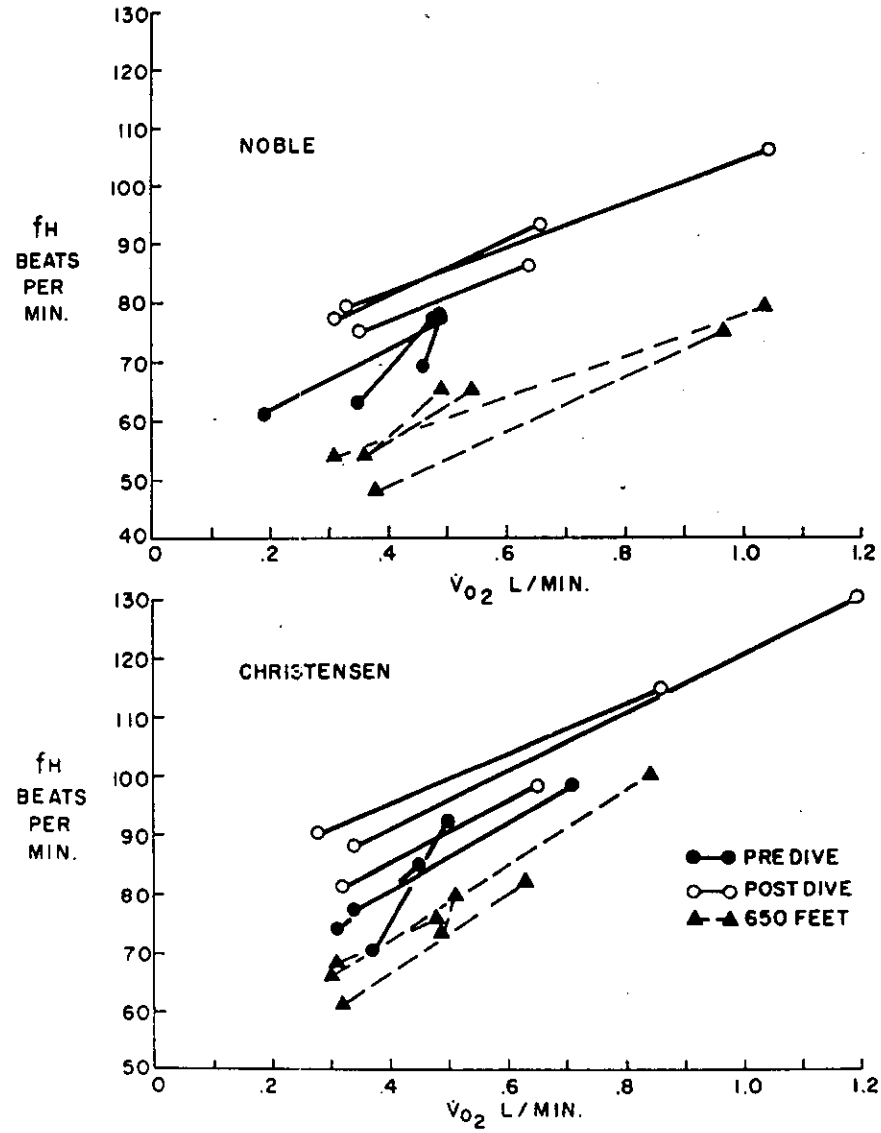

FIG. 119. Cardiac rate response to exercise. Points on the left end of each line are determined at rest, those on the right after 15 minutes of exercise.

in the post-dive period, and probably accounts also for the slight hyperventilation seen at the same time.

The bradycardia seen at depth is not easily explained. This finding is consistent among all heart rates taken with the subjects resting, including

rates determined from the clinical ECG's that were performed each day. Relative inactivity is a possible cause, but bed-rest experiments do not usually reveal much change in only two days (12). Bond has mentioned the possibility of a general metabolic "slow down" during prolonged submergence, but did not propose a mechanism or indicate the nature or magnitude of any actual metabolic change (1). It is not possible to judge whether the bradycardia is a direct pharmacological effect of the high helium pressure.

By inserting a large weather balloon in the breathing system as shown in Figure 120 and adjusting the system for rebreathing, it was possible to produce a controlled buildup of the subject's own CO_2. This provided the

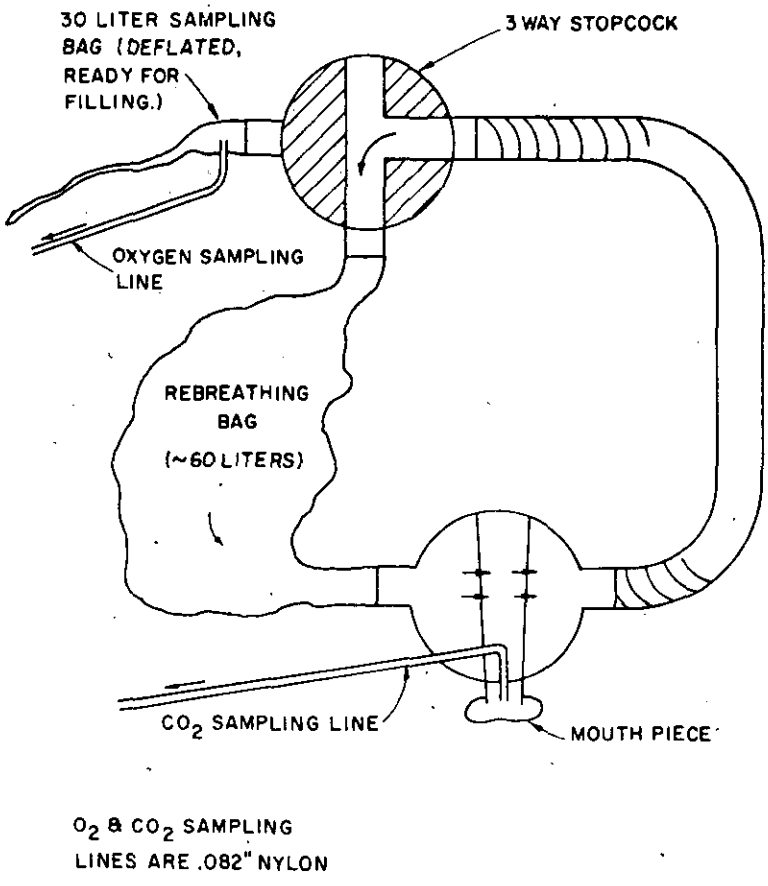

FIG. 120. Arrangement of apparatus for CO_2 response experiments. The breathing system was modified to include a rebreathing bag, to which oxygen was added to minimize hypoxic stimulus.

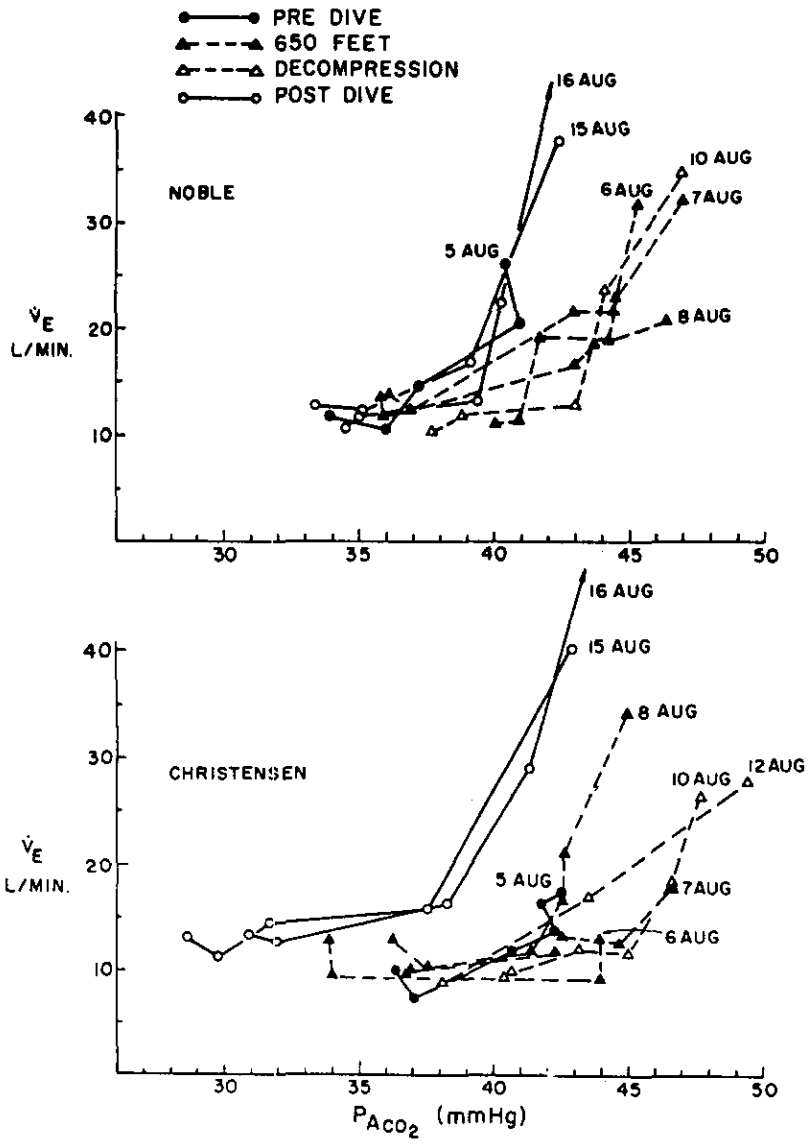

FIG. 121. CO_2 response curves, showing increase in respiratory minute volume as a function of alveolar CO_2.

basis for constructing CO_2-ventilatory response curves for use in a search for modification of respiratory reactivity to carbon dioxide. Sufficient oxygen was available in the chamber atmosphere to minimize the hypoxic stimulus in the experiments performed at pressure, and in the sea level experi-

ments extra oxygen was added to the rebreathing bag. After control runs the subject breathed from the rebreather until a definite increase was seen in end-tidal CO_2, at which time the stopcock was switched to the sampling bag for a timed volume measurement. During such a collection period the subject breathed a constant level of CO_2, since no new CO_2 was entering the rebreather at the time. This rebreathing procedure was repeated several times at increasing levels of end-tidal CO_2.

The results of these experiments are shown in Figure 121. The predominant finding here is a distinct shift to the right of the steep part of the response curves done at depth. Whether this is accompanied by a change in slope is not certain. Experiments by others, with added external resistance, have shown a change in slope along with a shift of the response curves similar to that observed here (2, 10). No definite time-related trends can be seen in these curves that might indicate accommodation to the environment. The rather low "resting" values of P_{CO_2} we feel were due to psychic stimulation, possibly combined with inadequate rest period before the beginning of measurements.

Summary

In two subjects exposed to the pressure equivalent of 650 feet, moderate exercise cause no increase in oxygen consumption and a slight rise in end-expiratory CO_2. The ventilatory response to exercise was much reduced, but the heart rate responded in a normal way. CO_2 response curves were shifted to the right, but showed little change in slope.

These experiments show that man can spend long periods of time at the depths of the continental shelves and can perform moderate physical work there. It is not known what the physiological limitations of deeper saturation diving will be.

Acknowledgment

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PREDICTION OF PHYSIOLOGICAL LIMITS TO HUMAN UNDERSEA ACTIVITY AND EXTENSION OF TOLERANCE TO HIGH PRESSURE

C. J. Lambertsen
Institute for Environmental Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA

Man exposed as a diver in the deep sea experiences, in all of his physiological systems, greater environmental forces and stresses than in any other sustained working situation. These forces drastically modify his physiological processes and his performance.

The continuing question to physiology is "What are the specific limits of tolerance to high pressures?" The answers to be obtained will involve the most fundamental mechanisms in physiology and biophysics.

THE PHILOSOPHY OF LIMITS

Physiological limits of many forms do exist for diving. They exist at all depths, from the shallowest to deep diving. Some limits can be overcome or postponed by modification of the diving method. Some can be masked. Some can be eliminated by engineering. Most persist and must reemerge with the increasing pressures and durations of deep diving.

Investigation and prediction of these limits require constant awareness of what diving actually is, in its many forms. The activity of diving is a linked composite of subconscious physiologic mechanisms which support the consciously purposeful functions (interpretation and thought, communication, work, manipulation) which are the intended aspects of diving. Diving is not simply passive exposure to gas pressure in a chamber, and it is not simply breathing or breath holding underwater. Therefore prediction of limitations must be concerned not only with the absence of convulsions or unconsciousness but also with the quality of thought and the capacity for useful physical action. The nature and degree of performance disruption can vary with any combination of sensory, mental, psychomotor and physical processes (Table 1). The disruptions can be of any degree, extending from undetectable to full physical incapacitation to unconsciousness.

Against this background it is the intent of this paper to offer the philosophy of limitations and prediction that has guided the Institute for Environmental Medicine's

series of Predictive Studies concerned with extending tolerance to work at high ambient pressures.

Oxidation	
Respiration	Sleep
Circulation	Rest
	Work
Sensation	
Mentation	
Manipulation	
Communication	

Table 1. Functional Components of Deep Diving.

The Diver

The working diver is unique in the spectrum of exposure to extreme physiological stress (Fig. 1). The athlete functions to physical exhaustion, but in an ideal and harmless environment. The astronaut is essentially unstressed, week after week, regardless of distance from earth, protected by engineering from most hazards or even need for severe exertion. The mountaineer suffers the cold and extreme hypoxia of Mount Everest, but after weeks of progressive adaptation prior to attempting his final ascent. Even the whale is not exposed to the full severities of human diving.

Fig. 1. Diver Breathing Helium-Oxygen Mixture While Performing Practical Work in Water-Filled Chamber at Pressure Equivalent to 488 Meters (1600 Feet of Sea Water) (8).

It does not have to ventilate its lungs, it has no narcotic, hyperoxic, decompression, temperature or strenuous exercise stress. Its exposures to hypoxia and pressure are acute, but the requirement for detailed performance is limited. For the human diver each of many forces or effects increases with the greater pressures of deep diving, and some increase with duration of exposure. Of all these examples he is the only one who becomes "physiologically" trapped by the high pressure environment and unable to leave it at will. It requires longer to decompress from saturation exposure to a helium pressure of 1000 feet of sea water than to return to earth from a lunar landing.

Fundamental Physiological Mechanisms Affected

In a search for limitations to deep diving it is not sensible to assume a precise pressure limit or a single limiting mechanism in any form of deep diving. The mammalian organism (mouse, man or whale) is infinitely complex. Moreover, the function of one process or system or organ or sensor or effector is intricately related to functions of other systems and processes. Ultimately all depend for their normal function upon fundamental biophysical and biochemical mechanisms, concerned with life factors of charge, reaction velocity, synthesis, binding and even physical diffusion of gases and ions.

Under the physical and chemical stresses of deep diving each of these many basic functions is a potential target, but all must differ greatly from each other in the conditions for producing initial disturbance (threshold ?) and also for rates of subsequent failure. It is even a large error to simplify the prediction of extreme pressure effects in diving by assuming that a specific site or structure is the primary limiting target. Even with equivalent effects upon the fundamental chemistry or membrane characteristics of many different cells, the measurable consequences of exposure can be expected to vary greatly. In great physiological systems, such as the entirety of our neurological assets, the more complex functions (with more components and steps in chemical and electrical activity) can be expected to fail at lower hydrostatic or gas pressures than will the simpler functions. The important study of impulse transmission in a peripheral nerve fiber or autonomic ganglion synapse will teach us the nature of their particular responses to pressurization. To learn of limiting effects upon judgment and vision it will be necessary to measure vision and judgment.

With this as general perspective it is clear that to learn the ultimate limits of diving requires two related forms of investigation and analysis. Fundamental mechanisms must be examined in any appropriate tissue or animal to hydrostatic and gas pressures well beyond those conceivably reachable by man. And man himself must be systematically examined, step-by-step, in minute physiologic detail under

conditions beyond those to be encountered in practical operations. Both approaches are honorable and absolutely necessary. There is no room for trial and error research in human exposure to environmental extremes.

PRIMARY STRESSES OF UNDERSEA ACTIVITY

A classical concept out of basic pharmacology and engineering is that response to a drug or physical stress is usually proportional to the drug dose or to the severity of the stress. The quantitative "dose-response" curve can often be used to describe basic cellular reactions or overall physiologic competence. It is the ideal predictive measure for specific effect and limitation. However, without precise quantitative studies no such predictions of limiting relationships can be described. Description is required for each function of interest, as affected by increasing degree of each stress of importance. Prediction derives from this description.

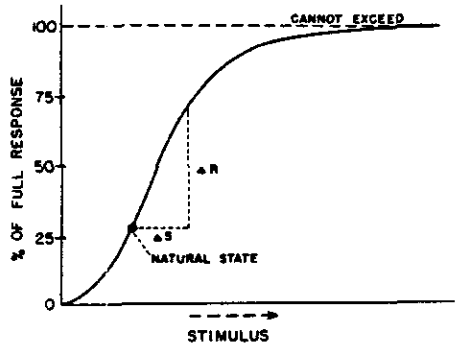

Fig. 2. Stimulus or Dose-Response Relationships in Physiology and Pharmacology

The Nature of the Stresses

The identities of several primary stresses are well known, even though their mechanisms and interactions are more conceptual than demonstrated. They include: Temperature, Physicochemical Effects of Inert Gases, Hydrostatic Pressure, Inert Gas Exchange, Hyperoxygenation, Hypoxia and Respiratory Gas Density. Each ultimately influences neural, circulatory, respiratory and other functions (Table 2).

Hypothermia	Hyperthermia
Hyperoxia	
Hypoxia	
Hypercapnia	
Hyperbaria	
Physicochemical Effects of High Inert Gas Pressure	
Communication Decrement	
Increased Respiratory Gas Density	
Respiratory Work	
Sleep	
Interactions	

Table 2. Major Pressure, Temperature and Atmospheric Stresses in Undersea Activity

Thermal Exchange

Temperature regulation, hypothermia and hyperthermia are the background factors against which nearly every other stress of undersea activity expresses itself.

Deep body temperature is a controlled component of the design of the internal environment of the mammalian organism, affecting such basic factors as hydrogen ion activity, calcium ionization, and the kinetics of numerous enzymatic reactions. Its control is not to be interfered with in diving.

Temperature is therefore of extreme practical limiting importance, regardless of depth, but not independent of it. Temperature deviations can be incapacitating or lethal or can contribute to lethal outcome in interactions with gas narcosis, very probably with hydrostatic pressure, and certainly with increased gas density. Search for tolerance to ambient temperature alteration is essential to the understanding of limitations of other stresses, and no study of effects of gases or pressure can ignore temperature as a critical variable.

Temperature stress increases severely with increasing ambient pressure, in water or in a gaseous environment. The compression of gas (e.g., helium) molecules increases heat capacity of the respired and ambient atmosphere, leading to excessive heat transfer between lungs and atmosphere or skin and atmosphere. Transfer may involve gain or loss of body heat, depending upon thermal differential between body and atmosphere. The result may be intolerable or incapacitating hypothermia or hyperthermia. Since this aspect of deep undersea activity involves physical exchange processes not adaptable to physiological modification, the limitations upon temperature regulation imposed by increased gas density and altered ambient temperature can be predicted to remain unless minimized by engineered systems for adjusting the temperature of ambient and respired gas. The precision of

regulation required for these systems increases with diving depth, and relates as well to forms of physical work and to individuals (Table 3). Even in dry, helium-filled chambers the spread of comfort temperature becomes close to 1°C at 1200 feet of sea water and, in the presence of physical activity, should be still less at still higher pressures. Temperature control is therefore a major technical component of any deep diving life support system. The real requirement is to eliminate temperature abnormality at all depths rather than to provide physiologic countermeasures in the presence of uncontrolled or abnormal body temperature.

Depth		Low Limit	High Limit
Meters	Feet	°C	°C
122	400	28.5	31.5
213	700	29.0	31.5
274	900	30.0	32.0
366	1200	32.5	33.5

Table 3. Thermal Comfort Ranges in a Helium Environment (1).

Physicochemical Effects of High Inert Gas Concentrations in Cellular Structures

It seems inevitable that at increasingly high pressures the increasing molecular concentration of any inert gas in cell structures will interfere with any function of any cell. The effects of inert gases are probably qualitatively numerous, even though the tendency persists in undersea physiology to designate "narcosis" as a single end result. The term "narcosis" is a loose one and it is very likely that the influence of high inert gas pressures is not a single one, even for a single inert gas. Effects upon membrane function, metabolic enzyme function and synthetic functions can all be conceived, with different dose-effect patterns, and different consequences or symptoms, with different gases. Inert gas effects on a retinal rod cell could affect vision. The same biophysical effect upon the smooth muscle cell of a retinal vessel could affect its contractility.

Gases differ in fundamental influence upon cell components. While nitrogen is distinctly narcotic at pressures less than 10 atmospheres, helium and neon produce no prominent depression of mental or sensory function at (38 ata pressure) 1200 feet of sea water (1). Since all indications are that inert gases should induce "dose-effect" patterns of functional change, it is probable but not at all certain that helium or neon will not induce disruptive effects on central nervous system function comparable in degree to those of nitrogen until ambient pressures much in excess of 3000 feet of sea water are experienced (1) (Fig. 3).

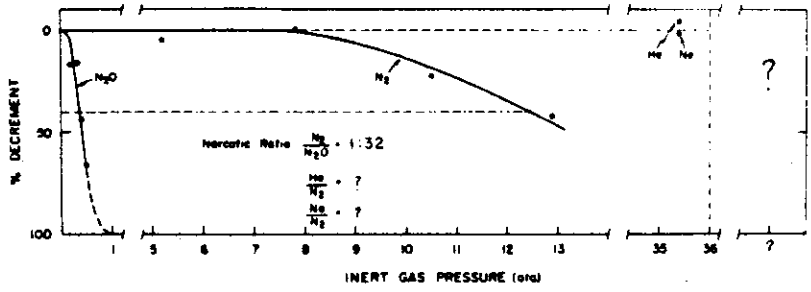

Fig. 3. Comparative Narcotic Effects of N_2O, N_2, Ne and He on Mental Function (Arithmetic Index) (1).

Faced with these forms of unawareness of the mechanisms of inert gas effects, prediction of limitations imposed by inert gases requires detailed study of individual gases over an extreme range of pressures. The true separation of helium and hydrostatic pressure effects will be extremely difficult in any specimen, and probably not possible in man.

Hydrostatic Pressure

Extreme increase in hydrostatic pressure itself is limiting, even without accompanying increase in solution of inert gases in tissues. Pressurization can produce myospastic immobilization, paralysis, convulsions, cardiac arrest and death in experimental animals (2, 3, 4, 5).

In man, "moderate" increase in hydrostatic pressure (e.g., to 10 meters of sea water) produces no clearly detectable effect. Higher pressures (e.g., 20 to 60 meters of sea water), especially when rapidly attained, induce increasing degrees of derangement, including temporary incapacitation (Fig. 4) (6, 7, 8). The bases for the varied symptoms and signs which include malaise, mental slowness, sleepiness, dizziness, nausea and vomiting, weakness, tremors and myoclonic spasms, and electroencephalographic changes (6, 7, 8, 11, 26), is not known. In the absence of an evident effect of helium itself (1), it is presumed that these derangements are due to hydrostatic pressure.

Since the most easily measurable effects of compression have been tremor and electroencephalographic changes, the designation "High Pressure Nervous Syndrome" has been applied to the pattern of abnormalities produced (6, 7). The term is useful but too specific for a phenomenon which is undoubtedly general in its effects, even on non-neural biological systems (9, 3, 10, 30, 31).

Limitations. Investigation of hydrostatic pressure effects has involved (a) study of rate and degree of compression in man to approximately 65 ata (11, 24), and (b) extension of hydrostatic pressure exposures to over 200 ata in animals and isolated tissues (12, 9, 10, 27, 28, 17, 16)

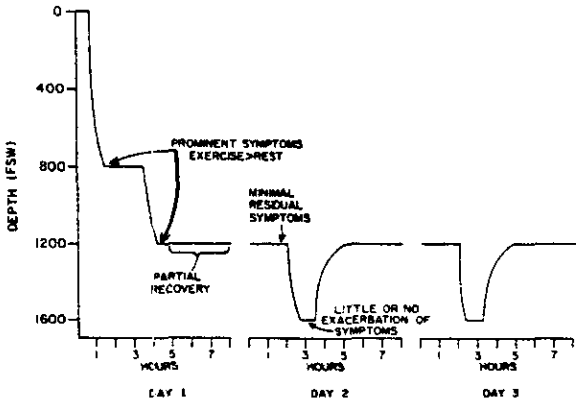

Fig. 4. Rapid Compression in Helium Atmosphere to Presure Equivalent of 244-366-488 Meters (800-1200-1600 Feet) of Sea Water (8).

Prediction of limits of tolerance to increased hydrostatic pressure requires the same philosophical reasoning as for the narcosis and/or oxygen toxicity encountered in diving. Each of these stresses must be considered as exerting effects on more than a single biophysical or chemical mechanism, at many sites and therefore on many functions (Fig. 5). Indication of multiple molecular sites for effects of hydrostatic pressure has actually been observed (12). While an obvious initial expression of hydrostatic pressure effect may be tremor, it should be considered that multiple, simultaneous other effects must be occurring during high pressure exposure. While within limits all such effects may be reversible, probably most still remain unidentified. Therefore, the desired dose-effect relationships have not been determined and prediction of limitations to hydrostatic compression in man is not now possible.

On gross and purely practical grounds it is evident from experiment in man with helium breathing that between 0 and 1200 feet of sea water no acute or lasting general handicaps develop when the rate of compression is slow or when a waiting period follows rapid compression (1, 6, 7, 8). Moreover, adaptation to rapid compression to this pressure appears to be complete (8), and in subsequent excursions from 1200 to 1600 feet of sea water general functions remain close to normal in spite of prolonged persistence of some electroencephalographic effects of compression (1, 13, 8). At helium pressures between 1600 and 2000 feet of sea water serious limitations of activity with helium breathing appear to persist for prolonged periods without full adaptation, even when compression is slow (11, 13, 14, 22, 30, 31).

The causes, the variety, and the reserve tolerance for these effects of hydrostatic pressure itself is not known. Therefore, at still higher pressures not yet fully explored in humans, it is not possible to predict which of many

PERFORMANCE
- PERCEPTUAL
- COGNITIVE
- PSYCHOMOTOR
- EXERCISE (AMBIENT GAS)
- WORK (UNDERWATER)

NEUROLOGICAL
- ELECTROENCEPHALOGRAM
- EVOKED POTENTIAL
- TREMOR
- POSTURAL FUNCTION
- ELECTROMYOGRAPHY
- NERVE CONDUCTION VELOCITY
- NEUROLOGICAL EXAMINATION

VISUAL
- ACUITY
- COLOR
- FIELDS
- EYE MOVEMENT

AUDIO-VESTIBULAR
- ELECTRONYSTAGMOGRAPHY
- AUDIOGRAM
- PHYSICAL EXAMINATION

METABOLIC
- O_2 CONSUMPTION
- CO_2 PRODUCTION
- RESPIRATORY EXCHANGE RATIO
- END-TIDAL P_{CO_2}, P_{O_2}

TEMPERATURE
- DEEP BODY TEMPERATURE (RECTAL)
- SKIN TEMPERATURES
- EXPIRED GAS TEMPERATURE
- ENVIRONMENTAL TEMPERATURE

ENDOCRINE FUNCTION
- URINE
- BLOOD

RESPIRATORY
- RESPIRATORY RATE
- TIDAL VOLUME
- EXERCISE RESPONSE
- DIAPHRAGMATIC ELECTROMYOGRAPH
- END-TIDAL P_{CO_2}, P_{O_2}

PULMONARY
- MAXIMUM VOLUNTARY VENTILATION
- FORCED VITAL CAPACITY (INSPIRATORY AND EXPIRATORY)
- VITAL CAPACITY
- TIDAL VOLUME
- INSPIRATORY CAPACITY
- EXPIRATORY RESERVE VOLUME
- FUNCTIONAL RESIDUAL CAPACITY
- RESIDUAL VOLUME
- TOTAL LUNG CAPACITY
- AIRWAY RESISTANCE
- LUNG COMPLIANCE
- ESOPHAGEAL PRESSURE

CARDIOVASCULAR
- ELECTROCARDIOGRAPH
- HEART RATE
- CARDIAC OUTPUT (IMPEDANCE)
- EXERCISE RESPONSE
- CIRCULATORY REFLEX

UNDERWATER WORK PERFORMANCE
- VIDEO RECORDING
- UNDERWATER RESPIRATION
- PERFORMANCE MONITORING

RENAL FUNCTION
- URINE VOLUME
- URINE COMPOSITION
- URINE ELECTROLYTES
- SERUM ELECTROLYTES

HEMATOLOGY
- COAGULATION STUDIES
- HEMOGLOBIN, HEMATOCRIT
- HISTOLOGY

Fig. 5. Scope of Correlated Measurements in Exposures to Rapid Compression, Breathing He-O_2 (8).

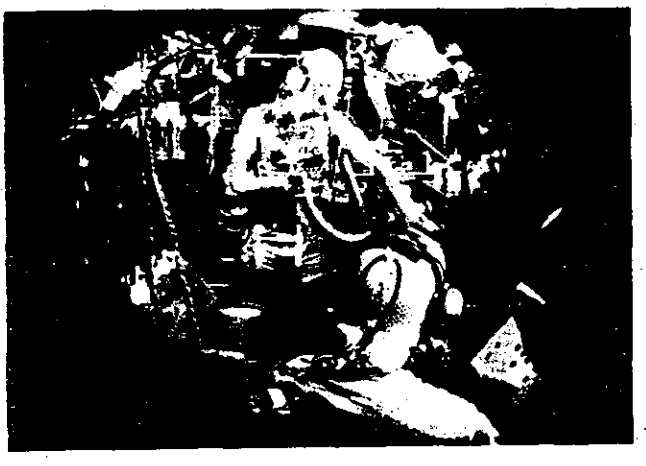

Fig. 6. Performance of Physiological Measurements During and Following Rapid Compression in a Helium-Oxygen Environment (Pressure Equivalent to 488 meters or 1600 Feet of Sea Water) (8).

affected functions have already reached their tolerable limits and which have only begun to be affected.

At the now relatively low pressures of 30 ata, where effects of helium itself have been shown to be innocuous (1), study of rapid rates of compression has indicated the occurrence of gross effects presumed to be due to the increasing hydrostatic pressure (8, 22, 30). Therefore, rapid compression to still higher pressures can be expected to induce more severe effects, including convulsions or other incapacitation. Prediction of tolerance to rapid compression requires consideration of the degree of compression, its rate and the patterns of time allowed for adaptation at stages during compression.

Extension of Tolerance to Pressure. Addition of narcotic substances (gases or other drugs) has been shown to prominently modify effects of very high hydrostatic pressure on isolated tissues (16) and in intact aquatic or terrestrial animals (5, 12, 15). Conversely, compression can at least partially overcome effects of depressant gases or drugs (2, 5). These classical findings in animals have been applied to undersea physiology, as by the addition of nitrogen to helium breathed by man at high pressure (22, 24, 25, 30), to increase tolerance to the effects of hydrostatic compression. Nitrogen modifies the pattern of effects produced by rapid compression (22, 24); it is not known whether it prevents or merely masks these effects (8).

Since determination of the scope and quantitative degree of effects produced by hydrostatic pressure alone and by compression with helium has been accomplished only in part, the specific influences of concurrent exposure to other inert gases along with helium cannot be defined. Any site of neurotransmission is a potential site where pressure or anesthetic may alter several functions (17). Some synapses are components of sensory or stimulant transmission pathways, others serve in depressant pathways. Since compression aggravates some neurophysiologic depressant effects of anesthetics and counteracts others, uniform or progressive benefit for all influences of compression cannot be predicted and is in fact unlikely. It therefore becomes necessary at pressures beyond those already explored for helium alone to "expect the unexpected" rather than simply to assume general amelioration of all compression effects.

This awareness is especially pertinent to neurological and respiratory effects of compression, since a convulsion in man at extreme gas density, with its composite of violent exercise and breathholding must inevitably result in death due to the failure to re-establish alveolar ventilation (35). The requirement therefore continues to exist for simultaneous study of critical physiological functions (Figs. 5 and 6) (8).

Inert Gas Exchange

There is as yet no indication that rate of uptake of inert gas during compression should be a limiting factor for ultimate diving depth (Fig. 6). Even if the concept of

osmotic forces related to local differential inert gas concentration (18) is eventually determined to have importance, its effects will most probably continue to be overshadowed by the more drastic influences of hydrostatic pressure. An exception, though not strictly limiting, is the arthralgia of compression which has been conceived as possibly related to osmotic influences of inert gas uptake (20).

Aspects of inert gas exchange will predictably continue at all pressures to be major limiting factors in decompression, in development of decompression sickness, in the multiple forms and consequences of isobaric inert gas counterdiffusion and in the therapy of decompression and isobaric sicknesses (23, 32). All of these attest to the physiological importance of inert gas exchange, and the necessary interactions among them make impractical prediction of definite improvement in safe decompression. It can be predicted that for each inert gas its exchange will continue to be governed by normal factors of anatomy, circulation, temperature and respiration, which themselves will continue to be limiting. Therefore the rates of inert gas elimination from critical sites are unlikely to be improved. For this reason it can be predicted that opportunities for extending diving without hazard of decompression or isobaric gas lesion diseases rests, not with a primary physiological speeding of gas elimination, but largely with (a) improvement in oxygen tolerance; and (b) improved understanding of the generation, growth and dissemination of gas bubbles, the interactions of bubbles and blood constituents, and the interplay among decompression, gas exchange, oxygen tolerance and isobaric gas exchange both in normal diving and in treatment situations.

Oxygen Toxicity and Oxygenation

Oxygen toxicity must be paired in importance with hydrostatic pressure in any ranking of major factors affecting predictions of ultimate diving capability. It presents limits to oxygenation as well as to attainable rates of inert gas elimination and effectiveness in "bends" therapy.

Oxygenation. At extreme pressures, beyond those yet reached by man, it has been considered on theoretical and indirect empirical grounds that large mammals are incapacitated through limitation of intrapulmonary diffusion of oxygen (19). This is not grossly evident in monkeys exposed to 100 ata or smaller mammals exposed even to 200 atmospheres and has not been found in man breathing dense gases at high pressures (1, 24), even in severe exercise (1).

Decompression and Isobaric Counterdiffusion. Extension of limits for excursion diving from saturation critically depends upon improvement in oxygen tolerance, as does increase in safety of decompression from each other form of diving, and improved therapeutic success in all forms of decompression sickness.

While substantial gains in extending oxygen tolerance are being made by programmed alternation of high and normal PO_2 (Fig. 7) (33, 34), prediction of further influence

upon diving depends in part both upon methods of oxygen use and upon resolution of the scope of acute and chronic effects of hyperoxia. Just as for narcosis and hydrostatic pressure, increased pressures and durations of supranormal oxygen exposure should be considered as causing multiple adverse effects upon multiple tissues. Determination of

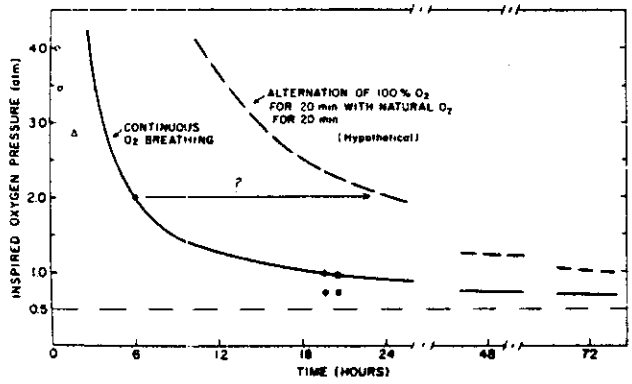

Fig. 7. Predicted Effect of Intermittent Oxygen Breathing on Pulmonary Oxygen Tolerance Limits in Man (34).

limits of oxygen tolerance and means for extending oxygen usage requires determination of the nature, onset, time course and reversibility of the several specific forms of enzymatic and related oxygen poisoning (34). Of critical importance is the determination of any as yet unquantified chronic or cumulative or residual effects of hyperoxia upon organs and their tissues.

Density of Respired and Ambient Gas

The linear increase in gas density which occurs with increasing pressure induces non-linear decrements in two forms of interchange between internal and external environments. It progressively modifies respiratory thermal exchange and ventilatory gas exchange, toward potential failure of each function.

Effects on Pulmonary Ventilation, Respiratory Control and Exercise Tolerance. Increased respiratory gas density increases respiratory resistance and work of breathing, with inevitable decrements in alveolar ventilation and capability for sustained effort by respiratory muscles. At any gas density each factor cited is related to the magnitude of pulmonary ventilation and hence to the degree and the duration of physical work being performed.

Tolerance to respired gas density has been extensively studied in man at increasingly high ambient pressures. In

the absence of prominent effects of hydrostatic pressure, acute exposure to increased gas density diminishes pulmonary ventilatory capacity in rest and in exercise (Fig. 8) (1, 20, 29). Such studies have indicated that density effects

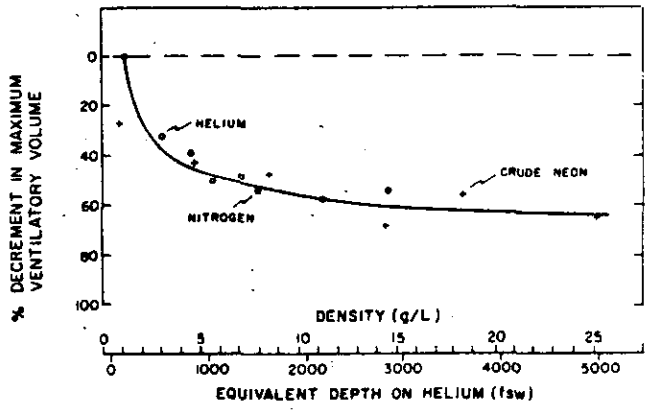

Fig. 8. Influence of Respiratory Gas Density and Airway Resistance on Ventilatory Capacity (1).

upon respiratory function (pulmonary ventilation and respiratory reactivity) at rest and in mild exercise should be tolerable even at gas density equivalent to helium breathing at 1500 meters (c.a. 5000 feet of sea water) (Fig. 9) (1).

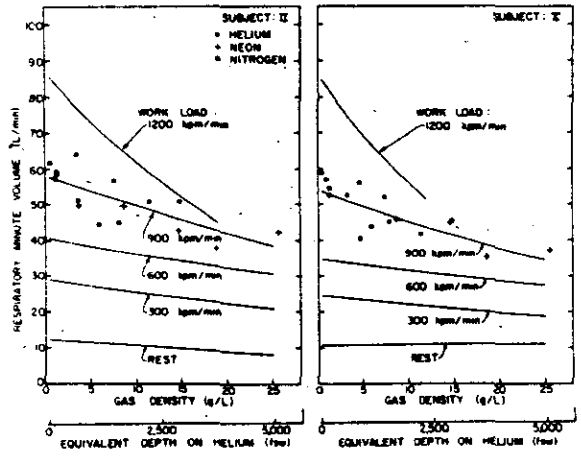

Fig. 9. Pulmonary Ventilatory Response to Exercise at Extreme Respiratory Gas Density (Equivalent to Helium-Oxygen Breathing at 1500 meters or to 1200, 2000, 3000, 4000, 5000 Feet of Sea Water) (1).

There is as yet no reason to revise this prediction for effects of gas density alone.

However, increase in gas density during compression in a helium atmosphere is inevitably accompanied both by increase in hydrostatic pressure and increase in any as yet unknown effect which may be produced by solution of helium in critical tissues. The interaction of such effects with the better defined influences of increased gas density appears to induce subjective respiratory distress not importantly associated with increased gas density at lower pressures (14, 21, 29). Precision in matching of method in such investigations should allow separation of density and

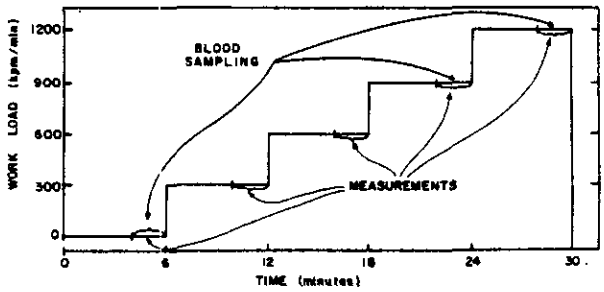

Fig. 10. Pattern of Continuous, Sustained, Increasing Workload in Studies of High Respiratory Gas Density (1).

pressure-related effects (Fig. 10). Since this separation is not now complete, prediction of diving limitations due to interactions of gas density and pressure now depends upon indications that even moderate exertion appears impractical in prolonged exposure to helium at pressures of 550 meters (1800 feet) of sea water (14). Since vigorous underwater work has been clearly shown to be practical in helium excursions to 488 meters (1600 feet) of sea water (8), a zone of sharply exaggerated decrement between 488 and 610 meters (1600 - 1800 - 2000 feet) of sea water breathing He-O_2 can be predicted. The subjective limitations encountered should be expected to be tolerable at rest, and to be magnified by increasing severity or duration of work. The degree to which these limitations are modified by use of gases other than helium must be quantitatively determined.

INTERACTIONS OF STRESSES AND EFFECTS

Throughout these considerations and predictions of physiological limits to pressurization, selected interactions of important stresses have been cited. Those interactions already mentioned are to be considered merely examples from an extensive pattern of inevitable cross-influences of physiological mechanisms, degrees of physical or mental activity, and severity of environmental forces. They include necessary interplay among work, oxygen pressure, gas den-

sity, exposure durations, hydrostatic pressure, temperature, inert gas and other factors (Fig. 11). They change qualita-

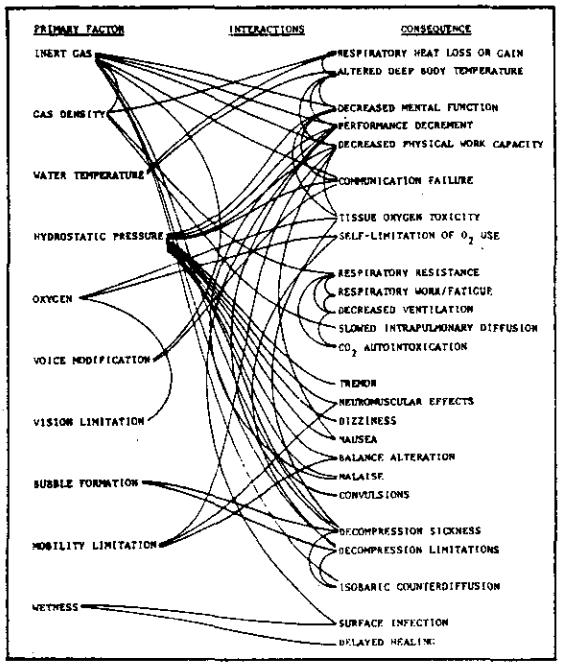

Fig. 11. Examples of Interacting Influences of Stresses and Effects in High Presure Exposures (35).

tively and in degree with increasing depth in the sea, and with duration of exposure. They confound any but gross prediction, making it necessary to explore men in controllable actual circumstances as well as to investigate basic mechanisms. Each stress alone can conceivably be tolerated better than can the composite of several or all stresses. The great progress of undersea physiology and activity of the past decade has derived from modification of the stresses and interactions (e.g., by choice of gas and compression rates, and improved life support systems) and not from modification of the basic physiological responses by drugs.

DETERMINATION, COMPENSATION, ADAPTATION, DETERIORATION

The fact that multiple limitations do exist to further extension of deep diving is less surprising than the fact that human pressurization to 122 to 615 meters (400-600-800-1000-1200-1400-1600-1800 and 2000 feet) of sea water, inconceivable very few years ago, has actually been possible. Extreme determination on the part of many of the "diver" subjects has allowed physiological exploration of the unknown in spite of sometimes severe symptoms.

Compensation and Adaptation

Part of the large advance, which has included sustained open sea diving operations at approximately 365 meters (1200 feet) of sea water, demonstration of underwater work capability at helium pressures to 488 meters (1600 feet) of sea water (8), and compressions breathing helium to 62 or nitrogen-helium mixtures to 65 ata, (11, 22, 24), has resulted from compensatory physiological adjustments, and from adaptation to the stresses considered in this analysis. The result of each of these mechanisms is a lessening of the biophysical, chemical or physiologic influences of the stresses, with restoration toward a stable condition of natural function and full competence. This restoration may include return of neural, smooth muscle, neuromuscular and other functions. Failure of partial degree may be expected to be followed by partial or complete adaptation, at least for some processes. Such adaptations will usually require time, and the time course cannot be expected to be the same for all functions and for all degrees of failure.

Limitation of further descent and/or more prolonged exposure to high pressure, with prominent decrement in physical or sensory or mental performance, is to be predicted when compensation and adaptation mechanisms become inadequate in overcoming the imposed individual or composite stress. At the limits of compensation and adaptation acute decrement can then be followed by progressive deterioration and failure of specific functions. This is the ultimate and potentially irreversible limitation to deeper or longer exposure.

Deterioration

In several situations exposure to the physical or toxic stresses of high pressure must predictably impose true limitations upon extension of diving depth. A proposed example is an increase in pressure and respired gas density to such a high degree that the work of breathing, even at rest, is severe. In this situation performance of useful physical activity will be impractical, even though discrete manipulation and sensory/mental functions are competent at rest. Continued excessive exertion by the muscles of respiration, even without considering the probable overlay of hydrostatic effects upon neuromuscular function, will necessarily result in progressive fatigue of these respiratory muscles, decompensation of the diaphragm and intercostal muscles and failure of ventilatory function (1, 8, 21). In the presence of hydrostatic pressure effects upon neuromuscular transmission or muscle contraction, the above-mentioned influences of gas density must inevitably be aggravated. This entire sequence must be exaggerated by any requirement for exercise, whether for practical purpose or emergency. Concurrent with this predicted respiratory deterioration, the act of sleep would predictably further diminish respiratory reactivity, accelerate the failure of ventilation and result in further hypoxia and hypercapnia.

Since decompression from prolonged exposure to high pressure cannot be rapid, any escape or withdrawal from a progressive respiratory decompensation can only be slow. The rate of withdrawal allowable by the requirements for inert gas elimination should be considered inadequate to allow recovery of capacity for ventilation. Continued deterioration, complete respiratory failure, severe hypoxia and death must therefore result (1, 8, 21).

At the limits of tolerance to extreme levels of respiratory gas density the use of pharmacologic therapy or substitution of another inert gas is not likely to overcome all effects of compression, even though it may mask some (8). Moreover, attempts to sustain survival at high gas density by hyperoxygenation should predictively further diminish ventilation while introducing oxygen toxicity as an additional respiratory complication.

The example is cited here again to indicate that, while capability for work at high pressures has been remarkably extended, limits of several forms can indeed ultimately be expected for rate and degree of compression, even if all factors but respiratory gas density and associated hydrostatic pressure are controllable. The limits must be expected to be more stringent in open sea operations than in laboratory chambers. At present, largely due to lack of quantitative knowledge concerning effects of hydrostatic pressure in man, it is not possible to project the depth range at which the irreversible respiratory failure described above should be considered inevitable. It surely exceeds 600 meters (or 2000 feet) at rest and may not be much greater for extended work.

CONCLUSIONS

Exposure of man to high ambient pressures has increased from the equivalent of approximately 100 to over 600 meters (300 to over 2000 feet) of sea water during little more than the past decade.

Detailed investigation of the physiologic influences of compression indicates that:

oxygenation will not be limiting at depths less than 1000 meters (c.a. 3000 feet).

increased respiratory gas density alone should be tolerable at rest at least to pressures equivalent to helium breathing at 1500 meters (c.a. 5000 feet), but will severely limit productive, sustained physical work at lesser pressures.

full functional competence for human physical, sensory and intellectual activity in water at depths between 365 and 610 meters (c.a. 1200 and 2000 feet) of sea water should be attainable.

the most clearly limiting stresses are hydrostatic pressure and temperature. In their

interactions with other stresses each is exaggerated and rendered unpredictably more limiting.

increased hydrostatic pressure with helium breathing induces prominent but ill-defined limitations upon physical activity and respiration at pressures between 490 and 550 meters (1600 and 1800 feet) of sea water. At 610 meters (2000 feet) of sea water neurological changes are sustained throughout exposure even at rest, and actual capacity for sustained physical work is not predictable.

decompression rates in saturation or excursion diving depend upon physical principles and will probably not be increased except by improvement in oxygen tolerance.

oxygen tolerance is susceptible to practical extension by programmed intermittency of exposure even though the several chemical mechanisms of oxygen toxicity will predictably remain active.

temperature limitation in diving will remain serious at all depths and will continue to impose extreme engineering requirements in open sea operation at pressures beyond 365 meters (1200 feet) of sea water.

the multiple and interacting influences of oxygen, hydrostatic pressure, inert gases and temperature upon fundamental cellular physicochemical and biochemical processes will continue to result in unpredictably changing patterns of limitation with increasing depth.

beyond 600 meters (c.a. 2000 feet) the composite effects of gas density and hydrostatic pressure upon respiratory function in sustained exposures can predictably result in progressive, inescapable hypoxia and hypercapnia, and irreversible respiratory failure in man, even at pressures tolerated in smaller animals.

the addition of narcotic drugs or gases to helium breathed at high pressures can be expected to diminish some symptomatic and neurologic expressions of hydrostatic pressure effects. Where this diminution is produced by masking rather than by prevention of the hydrostatic pressure effects, effects can be expected to re-emerge as pressure is further increased.

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Human Tolerance to He, Ne, and N_2 at Respiratory Gas Densities Equivalent to He-O_2 Breathing at Depths to 1200, 2000, 3000, 4000, and 5000 Feet of Sea Water (Predictive Studies III)

C. J. LAMBERTSEN, R. GELFAND, R. PETERSON, R. STRAUSS, W. B. WRIGHT, J. G. DICKSON, JR., C. PUGLIA, and R. W. HAMILTON, JR.

Institute for Environmental Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania 19104

LAMBERTSEN, C. J., R. GELFAND, R. PETERSON, R. STRAUSS, W. B. WRIGHT, J. G. DICKSON, JR., C. PUGLIA, and R. W. HAMILTON, JR. *Human tolerance to He, Ne, and N_2 at respiratory gas densities equivalent to He-O_2 breathing at depths of 1200, 2000, 3000, 4000, and 5000 feet of sea water.* (Predictive Studies viron. Med. 48(9):843-855, 1977.

This collaborative investigation (Predictive Studies III) was performed to determine effects upon man of acute exposure to increased gas densities simulating the breathing of helium with normal oxygen levels at ambient pressures to 5000 ft of sea water (fsw). Simulation was accomplished by administering gases at progressively increased ambient pressure, but without exceeding the actual increase in hydrostatic pressure beyond that equivalent to 1200 fsw (37 ATA). During the exposures, detailed studies were performed of respiratory-pulmonary function, exercise tolerance, psychomotor and mental performance, and the chemical and cellular characteristics of blood. Neon was employed as an inert respiratory vehicle for oxygen, both to provide the highest respiratory gas density and to extend the limited studies of its narcotic properties. Observations under the conditions cited indicated no abnormality (decrement) in mental function due to helium or neon breathing; at 1200 fsw, a less than expected influence of gas density upon pulmonary movement of gases, and the capability of performing limited periods of extreme physical work even when respiratory gas density reached levels equivalent to helium breathing at 5000 fsw. No pathological changes in blood chemical or cellular composition occurred. In the course of exposure of subjects to respiratory inert gases (nitrogen, neon) which differed from the inert gas of the stable ambient, pressurized environment (helium), severe cutaneous itching, dermal gas lesions and vestibular dysfunction developed. This is described elsewhere as a new gas lesion disease, the isobaric inert gas counterdiffusion syndrome (22).

THE FINDINGS REPORTED here represent the integrated combination of specific studies, conducted by collaborating investigators of several disciplines and different laboratories, brought together in common purpose to explore the ultimate limits of human capability in the deep undersea environment. This is the third in a series of such "Predictive Studies" concerned with response to the combined stresses imposed by increased ambient pressure (14,20,24,26).

The major stresses imposed by undersea work at extreme depths include the *physical* limitations upon pulmonary ventilation, the *pharmacological* effects of narcotic inert gases, the *physiological* effects of altered body temperature, the *biophysical* consequences of increased hydrostatic pressures, and the *composite* changes induced by these stresses in the systems for respiratory control, pulmonary function, purposeful exercise, and intellectual performance. While these stresses and their effects upon fundamental life processes must all increase with progressive increases in ambient pressure, and each compensatory mechanism must have its limits, no true limit has yet been demonstrated.

BACKGROUND

Thus far it has been possible for man to sustain exposures for many hours to helium pressures equivalent to 600 m of depth in the sea and for many days at pressures only slightly less than this. However, in searching for the ultimate limits of human tolerance to the undersea environment, it should nevertheless be considered inevitable that, when using helium or other respirable inert gases with oxygen at increasingly greater depths, pressures will be reached which will, eventually, produce physiological decompensations. These decompensations will involve failures not only of respiratory-pulmonary function but also of mental ability, physical work capacity, neuromuscular coordination and other critical functions. In searching out such failures, it can be anticipated that these several types of derangements and any adaptations to them will not occur at the same time or to the same degree at any particular high pressure.

Determination of the ultimate limits for effective human undersea activity imposed by these gas and pressure-related stresses is also severely handicapped by

the absolute requirement for slow decompression from prolonged or saturation exposures to gases at high pressure. This is because, as physiological or other difficulties are eventually encountered at great depth while breathing even a low density gas such as helium, the abnormalities will probably persist throughout the high-pressure exposure, including the multiday periods required even for the initial stages of "saturation decompression." Due to this requirement for slow decompression, it will not be possible to escape rapidly from the stresses which generated dysfunction or even damaging effects. Then, during such a period of continuous, unrelievable stress, additional deteriorations could occur to further aggravate changes initially induced by the original exposure to extreme pressure (24). The consequence of physiologically stressful exposures from which a requirement for slow decompression prevents ready escape could, therefore, be far more serious than more severe, acute stresses of more readily reversible circumstances.

This study endeavors to use gases to separate major variables in undersea physiology. It has involved determination of the influences of nitrogen, neon, and helium—each alone and superimposed upon a high ambient hydrostatic pressure—to simulate exposure to the high density of a helium-oxygen atmosphere at even more extreme ambient pressures, beyond the limits of any existing environmental chambers. By intensive study of the effects generated by the denser gas nitrogen at relatively low ambient pressures, and by neon at intermediate pressures, much of the pattern of events to be expected from influences of increased respiratory work at extreme depths a) should be separable from the potentially hazardous influences of extreme increase in hydrostatic pressure itself, b) can be conducted under background conditions of helium-oxygen breathing over an ambient pressure range which has already been demonstrated to be safe for extended periods of time, and c) can be elaborated under conditions where a safe escape from a decompensated state should be possible by simply returning to an ambient helium atmosphere on substituting it for nitrogen or neon.

The present report is intended as a summary of the composite program. It introduces the purposes, scope of investigation and procedures, and major consequences of the collaborative study. Details of each major component of the composite investigation are being presented in separate reports.

SPECIFIC CONDITIONS AND PHYSIOLOGICAL STRESSES

The overall study was aimed at controlled, "dose-response" investigation of the dominant stresses conceived to be associated with exposure to nitrogen, neon, or helium, and the combination of nitrogen or neon with helium at increased pressure. These have included:

a) Increase in respiratory resistance and work of breathing due to greater density of respired gas. Effects of changes in gas viscosity upon pulmonary function.

b) Limitation of exercise tolerance due to airway resistance, increased work of breathing and respiratory muscle fatigue, interference with alveolar ventilation or interference with intra-alveolar oxygen or carbon dioxide diffusion.

c) Inert gas narcosis leading to decreases in sensory acuity, intellectual function, motor coordination and manual dexterity. Exaggeration of inert gas narcosis by carbon dioxide retention, expected in exercise at extreme gas density.

d) Alterations of body fluid volumes associated with increased ambient pressure.

e) Development of tremor or other neurophysiological effects associated with hydrostatic forces in compression, and modifications of such neurophysiological effects during exposure to high partial pressures of inert gas.

The principal aims of the present study were to provide for: quantitative measurement during exposure to each inert gas at each of a sequence of increasing pressures of the gas (the dose-response study); cross-related interdisciplinary investigations (respiratory-pulmonary, metabolic, neurophysiological, chemical, phy-

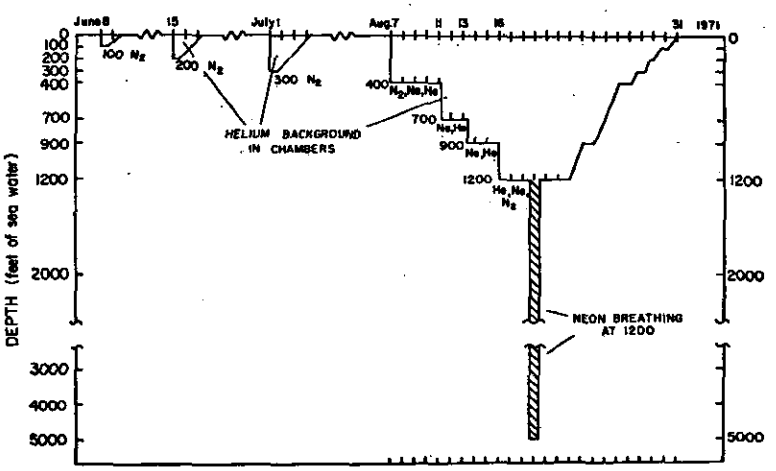

Fig. 1 Pressurization-exposure profile for series of dose-response exposures to N_2, Ne and He. Actual maximum pressure reached was equivalent to 1200 fsw. Shaded downward extension represents respiratory gas density equivalent to helium breathing at 2000, 3000, 4000, and 5000-ft depths, simulated by administration of N_2 or Ne with He at the stable 1200-ft pressure equivalent.

TABLE I. MEASUREMENT CONDITION: DEPTHS FOR EQUIVALENT GAS DENSITY.*

Nitrogen Series			Neon Series			Helium Series		
Dose-Response Condition	Density Ne	Equivalence He	Dose-Response Condition	Density N_2	Equivalence He	Dose-Response Condition	Density N_2	Equivalence Ne
0	18	167	0			0		
			18	0	167			
100	199	900						
141	272	1200						
						167	0	18
200	359	1558						
			272	141	1200			
300	529	2259						
400	699	2960	400	233	1786	400	32	72
			699	400	2960			
			900	536	3789	900	100	199
1200:			1200	—	5025	1200	141	272
326 N_2								
7 O_2	747	3159						
900 He								

*All values for Dose-Response Condition are expressed for practical comparative purposes as pressure equivalent of depth in "feet of sea water." 1 ATA = approximately 33 ft of sea water. Therefore, use the relationship

$$\text{ATA} = \frac{\text{Depth in Feet} + 33\ \text{Feet}}{33\ \text{Feet}}$$

for conversion to atmospheres absolute.

sical, cognitive, psychomotor); and direct, comparative study of the effects of three different inert gases (N_2, Ne, He) upon the same physiological functions under equivalent environmental conditions in the same subjects.

To meet these purposes, the program was designed to study systematically a group of normal men exposed to nitrogen with natural oxygen at ambient pressures equivalent to 0, 100, 200, 300 and 400 feet of sea water (fsw), and then also exposed to helium and crude neon ("neon 75" or 75% neon, 25% helium[1]) at 0, 400, 700 and 900 fsw (Fig. 1). The baseline ambient pressure was then increased additionally to a level equivalent to 1200 fsw, again with a natural partial pressure of inspired oxygen. During a several-day residence at this "depth," the subjects were further exposed for limited periods to respiration of neon at a high partial pressure, which permitted study of acute physiological and performance limitations at respiratory gas densities equivalent to helium-oxygen breathing at simulated depths to 2000, 3000, 4000, and 5000 fsw. Table I shows the diving depth equivalents for helium, neon and nitrogen as these gases were administered with natural oxygen pressure in the study.

For special purposes related to investigation of hydrostatic pressure reversal of narcosis, approximately 10 atm of nitrogen were included with the helium respired at the 37-atm maximum saturation pressure. On completion of each period of measurements during the composite nitrogen-helium or neon-helium exposures, the subjects returned to the ambient baseline helium-oxygen atmosphere simply by discontinuing the respiration of the other gases.

Four young men, each prominently involved in athletic activity, were selected as subjects. Physical characteristics of the subjects are illustrated in Table II.

Each subject had participated 1 year earlier in a 14-d exposure to elevated nitrogen pressures of 4 ATA (24). As was the pattern for that study, the subjects were selected for their high degree of physical, mental, and technical competence, and for exceptional motivation. The subjects were extensively trained, both physically and technically, during control phases at 1 atm prior to and during the initial pressurization phases at 100, 200, and 300 ft depth equivalents. Each subject-pair became an efficient, cooperative, and competitive subject-technician team whose work inside the sealed chamber was tightly and purposefully linked to the functions performed by individuals outside the chamber system. These high standards were considered necessary features of the experiment design, since a major purpose of the overall study was to probe the limits of human tolerance.

SCOPE OF STUDY

Table III indicates the scope of the series of investigations comprising the overall program. The four subjects were divided into two teams with a separate series of investigations for each team, but with complete matching of gases, pressures, temperature and other conditions of the program.

Table IV illustrates the individual components of each major study, with the major ambient pressure levels

TABLE II. SUBJECTS.

Team	Subject	Age (Years)	Height (cm)	Weight (kg)	Body Surface Areas (m^2)
A	II RB	19	192	89.1	2.21
	X TC	21	182	78.2	2.06
B	III TL	20	173	74.1	1.87
	V SK	21	193	84.5	2.16

FOOTNOTES

[1]Actual measured composition of gas used was 76.8% neon, 23.2% helium.

TABLE III. SCOPE OF PROGRAM.

Observations	Subject Teams
PULMONARY FUNCTION	A
Pulmonary Mechanics	
Dynamic Ventilation	
Gas Exchange	
Lung Volumes	
RESPIRATORY FUNCTIONS	A
CO_2 Reactivity	
Exercise Tolerance	
Respiratory-Blood Gas Exchange	
Metabolic Characteristics	
TEMPERATURE REGULATION	A+B
BLOOD CHEMISTRY AND ENDOCRINE FUNCTION	A+B
HEMATOLOGICAL CHARACTERISTICS	A+B
NERVOUS SYSTEM FUNCTIONS	
Central Electric Functions	A+B
Sensory Functions	A+B
Cognitive Functions	B
Tremor and Coordination	B
PSYCHOMOTOR PERFORMANCE	B
VOICE ANALYSIS	B

and the respired gas conditions under which specific measurements were made appearing in Table I. Details of the measurement apparatus and methods are represented in forthcoming separate reports of the major study components (e.g. Respiratory Control, Exercise Tolerance, Pulmonary Mechanics, Psychomotor Performance, etc.). The sequence of workloads imposed for the study of exercise tolerance is specifically illustrated (Fig. 2) because there have been several indications elsewhere (32) that physical work capacity at extreme hydrostatic and gas pressures will be grossly diminished. This sequence of uninterrupted periods of progressively increasing work used represented approximately 80% of the normal exercise capacity during air breathing at 1 atm.

ENVIRONMENTAL CHAMBER SYSTEMS

The chambers in which the studies were performed were part of a six-compartment environmental simulator system, equipped both as laboratories and as living compartments (Fig. 3). Control and measurement of temperature, gas movement, humidity, oxygen and inert gas composition, and lighting, together with chemical removal of carbon dioxide, provided baseline life support requirements. Locks provided for the transfer

TABLE IV. SPECIFIC MEASUREMENTS.

I. PULMONARY FUNCTION
- *Pulmonary Mechanics*
  - Airway resistance
    - Rest, exercise, forced ventilation
  - Flow resistive work of breathing
  - Respiratory pressures
    - Esophageal pressure, alveolar pressure
  - Compliance
  - *Maximum expiratory pressure flow*
- Dynamic Ventilation
  - Forced expiratory velocity
  - Forced inspiratory velocity
  - Maximum ventilatory volume
- Gas Exchange
  - Alveolar-arterial oxygen gradient
  - *Ventilation-perfusion*
- Lung Volumes-Exchangeable
  - Vital capacity
  - Dead space

II. RESPIRATORY FUNCTION
- Reactivity (CO_2 Response)
  - End-tidal P_{CO_2}
  - Respiratory frequency, depth and minute volume
  - Esophageal pressure
  - Work of breathing
- Exercise Tolerance
  - (6-min serial exposures to 300, 600, 900, 1200 kpm/min)
  - Physical performance
  - Metabolic characteristics
  - Pulmonary function in work
  - Ventilatory response in work
  - *Alveolar-blood gas exchange*

III. BLOOD CHEMISTRY, CELLULAR AND ENDOCRINE FACTORS
- Hematology-Cellular Characteristics
- Blood Chemical Composition
- Endocrine Studies

IV. NEUROPHYSIOLOGICAL FUNCTION
- Electroencephalogram
  - Rest
  - Exercise
- Evoked Brain Responses
  - *Auditory*
  - Somatosensory
  - Visual
- Tremor
  - Microtremor
  - Postural tremor
- Special Senses
  - Vision
    - Acuity
    - Color perception
    - Accommodation
    - Critical flicker fusion frequency
  - Taste
  - Hearing
  - *Vestibular function*

V. PERFORMANCE
- *Psychomotor Performance*
  - Gross coordination
    - Pursuit rotor
    - Bennett hand-tool dexterity test
    - Purdue pegboard
  - Fine coordination: small displacement tracking
  - Simple reaction time
  - *Manual tapping rate*
  - Muscle strength
    - Maximum grip strength
    - Strength estimation
- Cognitive Function
  - Paced arithmetic
  - Stroop test (rapid recognition task)
  - *Productive time estimation*
- Voice
  - Spectral analysis

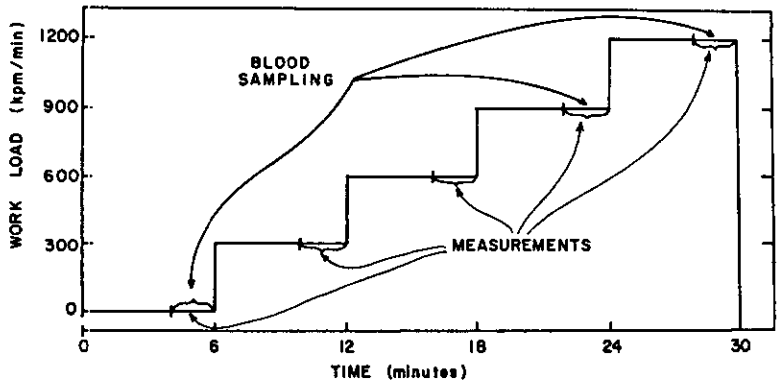

Fig. 2. Pattern of continuous, increasing workload performed by subject pair A under conditions of increasing ambient pressure, narcosis, and increasing respiratory gas density. Return to ambient respiratory gas environment followed 6-min rest period after exercise.

of equipment, samples, supplies, and food, including large equipment for experiments. Means were provided for electronically converting the distorted voice sounds originating in the high-pressure helium atmosphere to intelligible communication from subjects to external investigators. (Helium Speech Unscrambler, Helle Engineering, Inc., San Diego, Ca, Model WP-10H.) Compartments were equipped by the subjects for use as laboratories during the day and for residence at night. Shower and toilet facilities existed for personal hygiene.

One chamber, 8 ft in diameter and 12 ft long, was used by Subjects II and X and as the laboratory for exercise, respiratory, pulmonary, and blood measurements. Subjects III and V used an adjoining and connecting chamber, 6 ft in diameter and 8 ft long, for most of the electrophysiological and performance studies. During the last several days of decompression, all subjects were transferred to the larger, 10-ft diameter connecting chamber.

DECOMPRESSION

According to the planned sequence, decompression was accomplished as for saturation exposure to helium with oxygen. Details of the decompression procedure employed are provided in the Appendix, which indicates the time scale, gases breathed, and ambient pressure during the 8 d of the decompression period. Effective use was made of the shift to nitrogen-oxygen and oxygen breathing during late stages of return to 1 atm. Decompression-related observations are available from the Decompression Data Bank (5,28). To provide for desired measurements under conditions allowing separate examination of the respiratory-pulmonary effects of *density* and *viscosity* of respired gases, studies were performed at specific pressures, which were held stable during the decompression phase. These complementary studies carried out during the major compression or saturation stages are cited in the profile of Fig. 1.

Fig. 3. Environmental chamber system employed as pressurizable laboratories in study: Chamber 2 for exercise-pulmonary-respiratory-blood gas laboratory; chambers 3X and 3Y for neurological, sensory, and performance laboratory. Compartments were pressurized with a mixture of He and natural (0.21 ATA) O_2 at ambient pressures above 100-ft depth equivalent, where N_2 with 0.21 ATA O_2 was used. Both Chamber 2 and 3 systems were used at night for living spaces. Shower and toilet facilities functioned at all pressures. Food, supplies and samples were transferred by means of small pressure locks through walls of each compartment.

PHASING OF MEASUREMENTS

Fig. 4 indicates the pattern of experiment and measurement during a typical day in the series. Throughout the study, the step-by-step increases in ambient pressure were accomplished overnight or on nonworking days. Experiment periods, such as those shown for 400 fsw in the figure, were therefore always at a stable pressure.

SUMMARY OF RESULTS

It is the intent of this presentation to provide perspective and continuity for the overall program by summarizing the integrated findings from several components of the study of pressure and inert gas effects. Details of methods and findings will be elaborated for individual projects in specific reports, in which it will not be possible to describe general relationships of findings.

Pulmonary Function: With progressively increasing density of respired gas, whether helium, crude neon, or nitrogen with oxygen, an expected pattern of qualitative change in pulmonary function occurred (27,29), as encountered by others (31,32). Pulmonary work required to move respired gas increased as resistance to airflow became greater. The lungs themselves appeared unaffected, as indicated by unchanged pulmonary compliance. Capacity to rapidly move gas decreased, as measured by velocity of a single, forced exhalation or inhalation, as well as in terms of Maximum Ventilatory Capacity (Fig. 5 and 6).

An unexpected and important finding was that the degree of pulmonary ventilation limitation tended to become proportionately smaller as gas density became extreme. The result was that capacity for useful degree of ventilation was sustained to very high respiratory gas density (Fig. 6). This previously unrecognized advantage made possible the attainment of extremely high physical work levels without concurrently developing incapacitating pressures of alveolar carbon dioxide, which inevitably must occur when capacity for metabolic production of carbon dioxide exceeds that for alveolar ventilation.

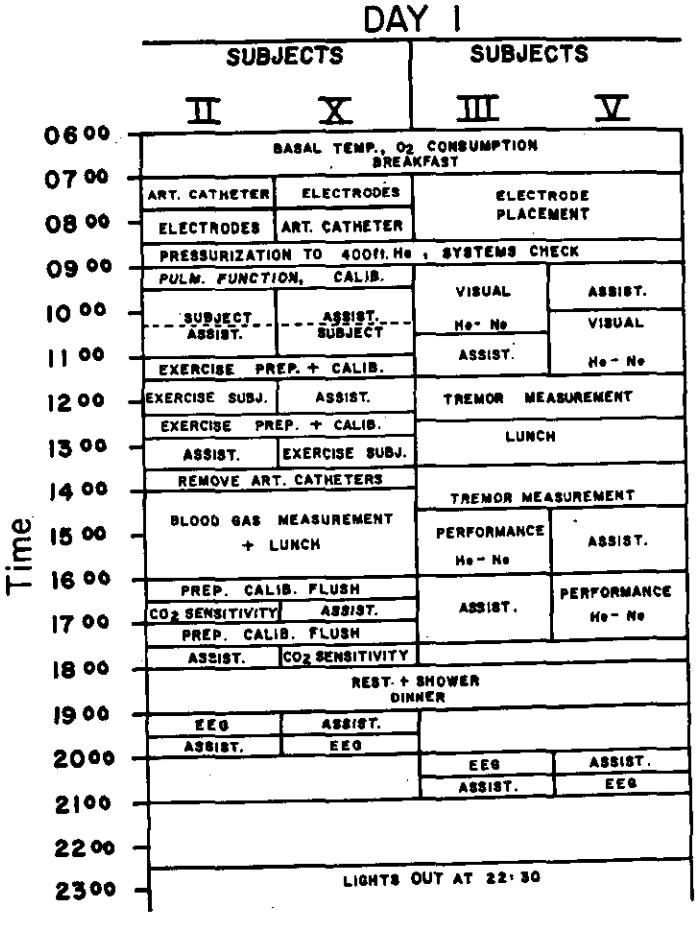

Fig. 4. Characteristic subject schedule of preparation and measurement: Day 1, 400-ft depth equivalent. Subjects alternated as subject and assistant throughout day, after insertion of vascular and esophageal catheters and application of electrodes. All electrodes and instrumentation were removed nightly except for sleep electroencephalograph electrodes.

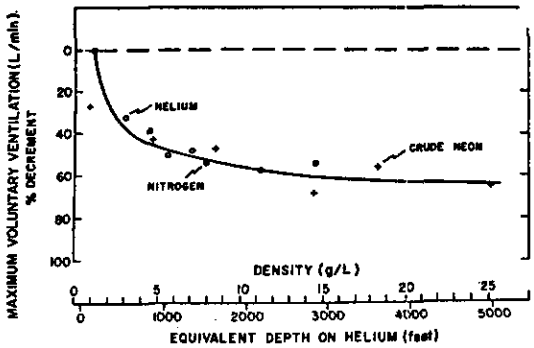

Fig. 5. Peak (maximum) expiratory gas flow rate as a function of breathing gas density. Measurements obtained as highest flow rate recorded in the course of forced vital capacity. Mean values in Subjects II and X.

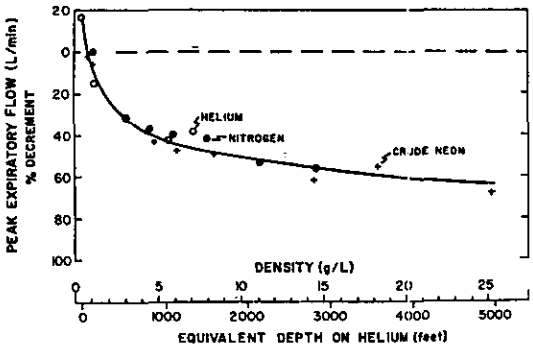

Fig. 6. Effect on maximum voluntary ventilation of increased ambient pressure and respiratory gas density. Mean results in Subjects II and X. Because density of crude Ne is nearly five times that of He, the respiration of crude Ne at a 1200-ft depth equivalent was used to simulate density effects to be expected with He at greater depths, to 5000 fsw.

Respiratory Control: Ventilatory response to rebreathing autogenously-produced carbon dioxide was progressively reduced as the density of gas breathed was increased (Fig. 7). This prominent reduction in total and alveolar ventilation was not found to be correlated with narcotic properties of the inert vehicle gases (He, Ne, N_2) but rather with the same factors of density, pulmonary resistance, and respiratory work that limited pulmonary dynamic function at increased ambient pressure. Therefore, the diminished ventilation is not to be interpreted as indicating narcotic depression of the respiratory neurons. These, most probably, were highly reactive but with their reactivity masked by resistance to gas flow in the lungs.

Respiratory Gas Exchange: Indwelling vascular catheters, inserted daily, permitted blood sampling at preplanned phases of the study (Fig. 2). Through measurements of arterial blood gas tensions at pressures to 400 fsw and venous blood sampled from the heated hand to 1200 fsw, it was learned that no detectable interference with oxygen or carbon dioxide exchange oc-

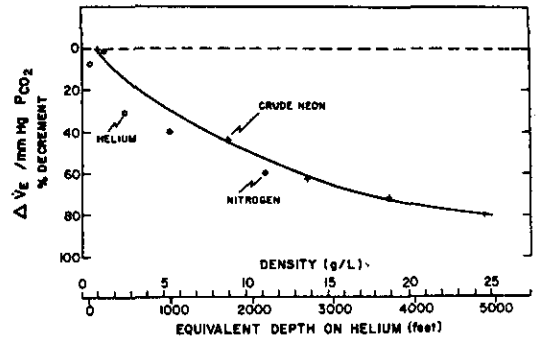

Fig. 7. Effect on ventilatory response to CO_2 at increasing ambient pressure and increasing breathing gas density. "CO_2 sensitivity" is depicted as: change in respiratory minute volume produced per mm Hg increase in end-tidal P_{CO_2}. Elevation of inspired P_{CO_2} induced by rebreathing expired gas, with controlled inspired P_{O_2} (15a).

curred at rest or in exercise with nitrogen to 400 ft, helium to 1200 ft, and neon to 900 ft. Blood sampling failed to be accomplished for neon breathing at the 1200 ft depth equivalent. The postulated diffusion limitation at extreme gas density or pressure (9,10), therefore, was not confirmed.

Exercise Tolerance: Completion of the increasingly severe pattern of exercise on a bicycle ergometer represented performance at approximately 80% of work capacity at 1 atm. Failure to complete this work occurred in only two conditions of the overall study and for two different reasons. One form of failure, by two subjects, occurred within 2 min of completing the most severe work level during nitrogen-oxygen breathing at the 400-ft depth equivalent. This failure was very evidently due to mental confusion and muscular incoordination induced by nitrogen narcosis. It was not a result of either dyspnea of respiratory-pulmonary limitation or of muscular fatigue in the exercising limbs.

The second form of failure, again by two subjects, occurred during breathing of the crude neon gas, again at the last 2-min period of the maximum workload. This failure to complete the planned sequence was due to high density of the respired gas. It occurred only under a condition equivalent to performing heavy work at a respired gas density equivalent to that to be expected with helium at a depth of 5000 ft, or with hydrogen at 10,000 fsw (Fig. 8,9). The degree of elevation of alveolar carbon dioxide pressure encountered in this situation was prominent (about 60 mm Hg) but was not in itself limiting.

Respiratory minute ventilation was evidently diminished with increasing respiratory gas density at each level of work. The degree of this ventilatory interference became severe at 1200 kpm/min, where exercise ventilation very closely related to maximum ventilatory capacity. At the more moderate work levels of 300 and 600 kpm/min, ventilatory function was symptomatically not difficult and maintained alveolar (end-tidal) levels of P_{CO_2} below 50 mm Hg.

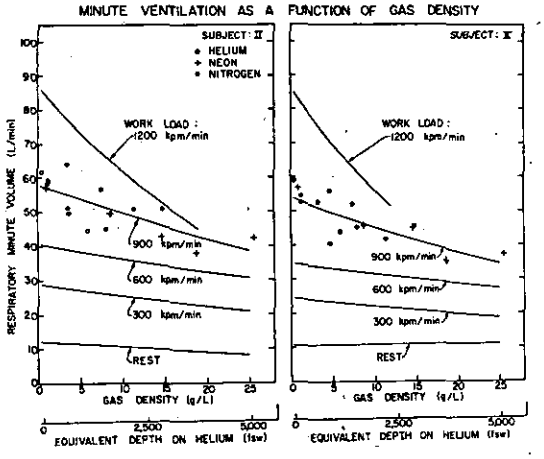

Fig. 8. Respiratory minute ventilation at increasing workloads and at increasing respiratory gas density. Separate findings in Subjects II and X. Individual data for different gases and ambient pressures shown only for 900 kpm/min. Final 1200 kpm/min work period clearly becomes limiting as respired gas density increases to equivalent of 2500-ft depth breathing He.

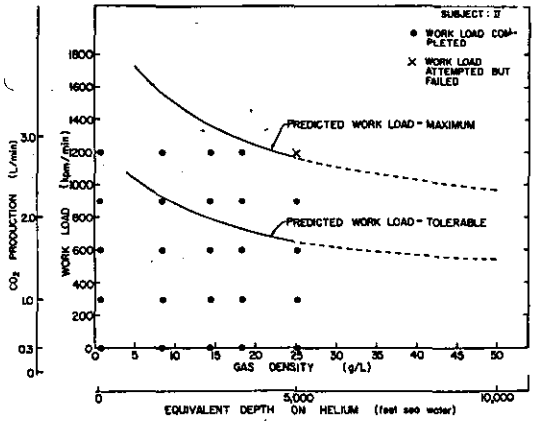

Fig. 9. Prediction of workload tolerable in exposure to increased respiratory gas density or undersea depth. Grid of black dots represents actual conditions of present study, with five levels of gas density at each of five levels of rest and work. The symbol X represents the condition in which failure occurred due to excessive respiratory resistance and work (maximum density together with final and maximum work period). Curve labelled "predicted workload-maximum" is actually not different from that which would induce ventilation equivalent to maximum voluntary ventilation at the indicated respiratory gas densities. The curve indicating "predicted workload-tolerable" represents composite circumstances of workload and gas density which do not result in alveolar P_{CO_2} elevation above 60 mm Hg.

On the basis of such findings it is predicted that the respiratory and pulmonary function required at rest and in support of moderate physical work, intelligent activity, and manual dexterity should be possible at or beyond these very great depths. With such indications, it now remains to be learned how and where factors other than gas density (hydrostatic force, narcotic or other pharmacological effects of inert gases, diffusion limitation) introduce truly detrimental effects upon physiological systems and purposeful activity.

Neurophysiological Changes: Probably because of the slow, stepwise compression over several days to the maximum 1200-ft pressure depth equivalent, no clear indication of a "high pressure nervous syndrome" (4,

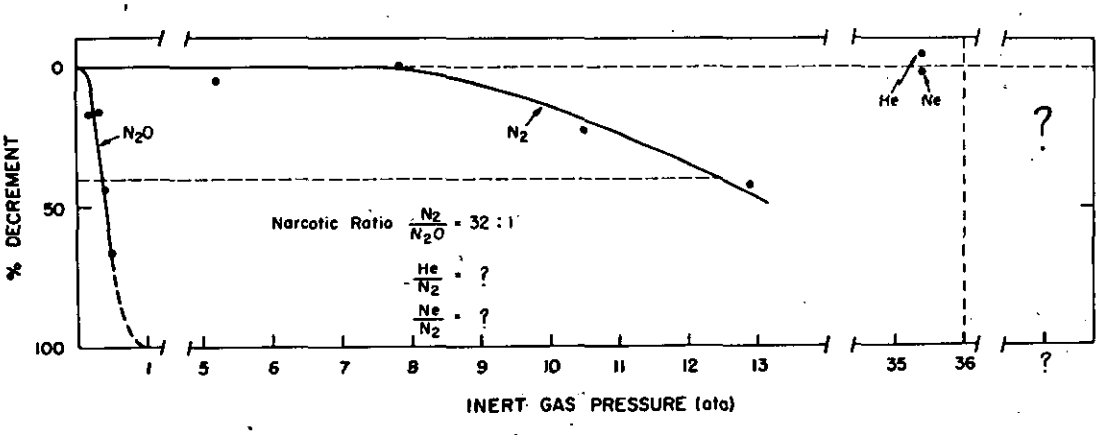

Fig. 10. Comparative effects of N_2O, N_2, Ne, and He upon a mental function (paced arithmetic). Mean values in Subjects III and V. Since previous study had demonstrated that N_2O at inspired pressures to 0.5 ATA induces prominent decrement in mental arithmetic skill (12), this effect was used as a basis for comparison of N_2, Ne, and He. Subjects were remarkably competent during N_2 breathing to nearly 8 ATA (about 230 fsw), and showed a N_2:N_2O *narcotic ratio of 32:1 while retaining considerable capacity for* mental function even to an inspired nitrogen pressure to 13 ATA (equivalent to 500-ft depth breathing air). The subjects were fully competent, without evident narcosis, during Ne and during He breathing to 37 ATA (1200 fsw). This indicates that any appreciable "narcotic" depression by Ne or He would not now be expected until depths probably more than twice 1200 ft are reached.

7,8,15) was observed throughout this entire study. Tremor measurement and spectral analysis of it showed only normal activity or minor deviations (30). Measurement of electroencephalographic activity and frequency analysis of the recordings showed no abnormalities at rest and no evident abnormalities even in the severely narcotized, exercising subject. Visual, auditory, and somatosensory-evoked electrocephalographic potentials indicated no important abnormalities, except in the most definite narcosis (nitrogen-oxygen breathing at 400 ft depth equivalent). Visual function was not detectably altered by any condition of the study. Taste sense was not modified by gas or pressure. Hearing was normal following the composite exposure, but vestibular function was unilaterally inactivated or subnormal in three subjects who developed the "isobaric gas counterdiffusion syndrome" (22).

Mental Function: Using cognitive tests previously employed to define the dose-effect depression of mental functions by nitrous oxide (12), no detectable mental decrement was found with either helium or crude neon breathing at 37 ATA. Nitrogen did produce a progressive central nervous system depression which, as expected (1,2,13), became prominent at pressures equivalent to 300 and 400 fsw. In Fig. 10, performance in paced arithmetic tests is shown for all pressures of nitrogen, neon and helium used, compared with effects of N_2O breathing in the same subjects. The figure indicates that, by comparing equivalent degrees of functional decrement produced by N_2O and N_2, a ratio of narcotic potency of N_2O and N_2 can be derived. This was found to be 32:1. Because mental function was normal at the highest pressure (37 ATA), it was not possible to detect any antagonism of pressure effect by the actual use of narcotic nitrogen for this purpose (19).

Psychomotor Function: Determination of change in manual dexterity, coordination, and reaction time indicated a definite decrement only during nitrogen breathing at pressures equivalent to 300 fsw or greater. Thus, neither neon nor helium significantly modified any of the psychomotor performance measures employed (18).

Temperature Stress: In the multi-day, stable phase of exposure to helium at increased ambient pressures, the subjects collectively selected temperature for comfort. The mean selected temperature became higher as helium density rose, with a narrowing of the comfort range (Table V).

TABLE V. THERMAL COMFORT RANGES SELECTED.

Depth (fsw)	Low Limit (°C)	High Limit (°C)
400	28.5	31.5
700	29.0	31.5
900	30.0	32.0
1200	32.5	33.5

An average weight loss of 2 kg occurred over the 11 d of exposure to helium at 37 ATA, in spite of a caloric intake averaging approximately 3500 cal/d. Since basal oxygen consumption was not consistently elevated, the degree of any thermal stress was not sufficient to expand metabolic activity.

Blood Chemical, Cellular, and Endocrine Characteristics: The combined influences of increased hydrostatic pressure, prolonged exposure to helium at increased partial pressure, and intermittent exposure to respiratory gases of increased density produced no physiologically important changes in blood electrolyte, blood cellular composition, catecholamine, or adrenal cortical hormone excretion as compared with pre-exposure controls or with prolonged exposure to increased nitrogen pressures (3,25).

UNEXPECTED FINDINGS

Isobaric Inert Gas Counterdiffusion Syndrome: In the course of performing the integrated investigations described above, urticaria, gas-filled skin lesions, and vestibular dysfunction developed. These pathological changes, described in detail elsewhere (11,16,21,22), occurred when nitrogen-oxygen, nitrogen-helium-oxygen, or neon-helium-oxygen was breathed while the subjects were surrounded by helium with natural oxygen pressure. Each form of lesion was incapacitating, although the urticaria and the dermal gas lesions were entirely preventable on most of the skin surface by use of a suit ventilated by the gas breathed (22). Occurrence of cutaneous itching and lesions had been observed previously by other investigators (6), who did not associate the phenomenon with development of gas bubbles in the dermal tissues. The unexpected finding, designated "isobaric gas counterdiffusion" (17,22), has been identified as a gaseous supersaturation generated by unequal rates of inert gas counterdiffusion, at a stable ambient pressure (isobaric state), with continuous evolution of gas bubbles in skin and continuous venous embolization of gas from subcutaneous capillaries to the heart and systemic circulation (11,17,22). It has been deduced from subsequent studies that the most probable basis for vestibular derangement itself was produced not by embolization but by gas bubble generation in the inner ear fluids, as a result of local gas counterdiffusion across the round window, from middle ear to the cochlear fluids (23). These drastic, unexpected findings are further considered to represent a potentially lethal condition. They appear to be fully preventable by avoiding circumstances involving counterdiffusion, either at local sites or over the entire body.

COMPOSITE EFFECTS

It was clear from the results of all studies performed that no detectable chemical or physiological handicaps accompanied prolonged exposure to a helium-oxygen atmosphere at a pressure equivalent to 1200 fsw (37 ATA). The subjects were capable of carrying out mental or physical functions essentially as well at this high ambient pressure as at their normal 1 atm environment. Furthermore, neon used as a respiratory inert gas imposed no detectable narcotic influences upon higher mental functions.

When respiratory gas density was grossly increased by use of crude neon or nitrogen as the respiratory

vehicle for oxygen, respiratory and pulmonary competence was preserved at rest. Respiration was accomplished even in exercise almost to the subject's demonstrated maximum exercise tolerance, and to a density of respiratory gas equivalent to helium-oxygen breathing at 5000 fsw. These findings indicate that there should be no decrement in pulmonary ventilatory function which would handicap further extension of man into the deep sea. Attention can, therefore, be turned to pharmacological influences of gases and to the influences of hydrostatic pressure itself.

ACKNOWLEDGMENTS

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METRIC CONVERSION FOR DEPTH AND PRESSURE
(1 m = 3.3 ft 1 atm = 10.08 msw = 33 fsw)

Experiment Design Parameters	Metric Equivalents	
Depth in Feet of Sea Water	Depth in Meters	Pressure in ATA
100	40.6	4.0
200	71.2	7.1
300	101.7	10.1
400	132.3	13.1
700	223.9	22.2
900	285.0	28.3
1200	376.6	37.4
2000	621.0	61.6
3000	926.4	91.9
4000	1231.9	122.2
5000	1537.4	152.5

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(See Appendix on the following two pages)

APPENDIX

PREDICTIVE STUDIES III — SATURATION-DECOMPRESSION PROFILE

This transcript describes the decompression to sea level of the four subjects following their helium-oxygen saturation exposure and transient exposures to neon and nitrogen at 1200 fsw. The transcript is written in a version of the PENNDEC Exposure Language used by the International Decompression Data Bank for the reporting and computer processing of pressure-undersea compression/decompression exposures (28). The periodic "stops" during the decompression were for the performance of experiments under the overall program. During these experimental periods, some of the subjects breathed gas mixtures other than the chamber gas for brief periods of time. It is felt that this had no important bearing on the decompression; the gas mixtures and time breathed have therefore been excluded for brevity. This information is available from the Decompression Data Bank upon request.

PENNDEC TRANSCRIPT

START EXPOSURE IDENTIFICATION=(PREDICTIVE STUDIES III) MODE=4
DEFINE PERSONNEL: X II V III
REMARK: DECOMPRESSION PROFILE FOR PS III

TIME (MIN)	PERSONNEL LIST	CHANGE KEY	DEPTH (FSWG)	INSPIRED GAS
DEFINE GAS: CHAMBER GAS 1 O_2=1.6% N_2=0% He=BALANCE				
0	ALL	LEAVE	1200	CH GAS 1
		REMARK: DECOMPRESSION RATE 6 MIN/FT		
1801	ALL	REACH	900	CH GAS 1
		REMARK: 18 HR 59 MIN HOLD AT 900 FT FOR EXPERIMENTS		
2940	ALL	LEAVE	900	CH GAS 1
		REMARK: DECOMPRESSION RATE 6 MIN/FT		
4201	ALL	PASS	690	CH GAS 1
		REMARK: O_2 IS ADDED GRADUALLY OVER AN 8 HR PERIOD TO INCREASE PERCENT FROM 1.6% TO 3.0%		
DEFINE GAS: CHAMBER GAS 2 O_2=3.0% N_2=0% He= BALANCE				
4685	ALL	PASS	610	CH GAS 2
5341	ALL	PASS	500	CH GAS 2
		REMARK: DECOMPRESSION RATE CHANGED TO 7 MIN/FT		
6041	ALL	REACH	400	CH GAS 2
		REMARK: 23 HR 52 MIN HOLD AT 400 FT FOR EXPERIMENTS		
7473	ALL	AT	400	CH GAS 2
		REMARK: DURING LAST 47 MIN OF HOLD AT 400 FT O_2 IS INCREASED GRADUALLY FROM 3.0% TO 6.0%		
DEFINE GAS: CHAMBER GAS 3 O_2=6.0% N_2=0% He=BALANCE				
7520	ALL	LEAVE	400	CH GAS 3
		REMARK: DECOMPRESSION RATE 7 MIN/FT		
8219	ALL	REACH	300	CH GAS 3
		REMARK: 8 HR 55 MIN HOLD AT 300 FT FOR EXPERIMENTS		
8754	ALL	LEAVE	300	CH GAS 3
		REMARK: DECOMPRESSION RATE 8 MIN/FT		
8977	ALL	REACH	272	CH GAS 3
		REMARK: 1 HR 32 MIN HOLD AT 272 FT FOR EXPERIMENTS		
9069	ALL	LEAVE	272	CH GAS 3
		REMARK: DECOMPRESSION RATE 8 MIN/FT		
9647	ALL	REACH	200	CH GAS 3
		REMARK: 6 HR 13 MIN HOLD AT 200 FT FOR EXPERIMENTS		
9987	ALL	AT	200	CH GAS 3
		REMARK: DURING LAST 33 MIN OF HOLD AT 200 FT O_2 IS INCREASED FROM 6.0% TO 10.0%		
DEFINE GAS: CHAMBER GAS 4 O_2=10.0% N_2=0% He=BALANCE				
10019	ALL	LEAVE	200	CH GAS 4
		REMARK: DECOMPRESSION RATE 9 MIN/FT		
10317	ALL	REACH	167	CH GAS 4
		REMARK: 1 HR 2 MIN HOLD AT 167 FT FOR EXPERIMENTS		
10379	ALL	LEAVE	167	CH GAS 4
		REMARK: DECOMPRESSION RATE 9 MIN/FT		
10614	ALL	REACH	141	CH GAS 4
		REMARK: 1 HR 34 MIN HOLD AT 141 FT FOR EXPERIMENTS		
10708	ALL	LEAVE	141	CH GAS 4
		REMARK: DECOMPRESSION RATE 9 MIN/FT		
11076	ALL	REACH	100	CH GAS 4
		REMARK: 11 HR 48 MIN HOLD AT 100 FT FOR EXPERIMENTS		

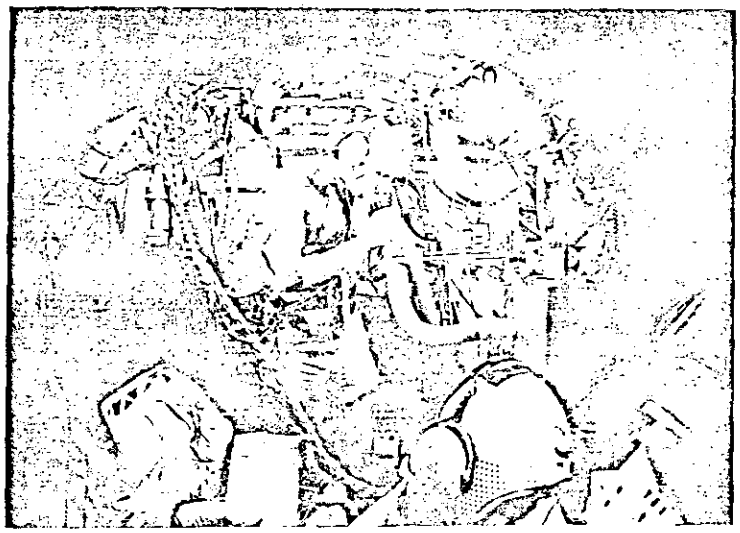
TIME (MIN)	PERSONNEL LIST	CHANGE KEY	DEPTH (FSWG)	INSPIRED GAS
11708	ALL	AT	100	CH GAS 4
		REMARK: 1 HR 16 MIN BEFORE RESUMING DECOMPRESSION SUBJECTS TRANSFER TO CHAMBER FILLED WITH AIR		
11784	ALL	STEP	90	AIR
11829	ALL	STEP	80	AIR
11880	ALL	STEP	70	AIR
11934	ALL	STEP	60	AIR
11999	ALL	LEAVE	60	AIR
		REMARK: DECOMPRESSION RATE 1 MIN/FT		
12009	ALL	REACH	50	AIR
12073	ALL	AT	50	O_2
		REMARK: SUBJECTS BEGIN FIRST PERIOD OF OXYGEN BREATHING BY MASK		
12074	ALL	LEAVE	50	O_2
		REMARK: DECOMPRESSION RATE 1 MIN/FT		
12084	ALL	REACH	40	O_2
12124	ALL	AT	40	AIR
12169	ALL	LEAVE	40	O_2
		REMARK: DECOMPRESSION RATE 1 MIN/FT		
12179	ALL	REACH	30	O_2
12209	ALL	AT	30	AIR
12249	ALL	AT	30	O_2
12279	ALL	AT	30	AIR
12315	ALL	LEAVE	30	O_2
		REMARK: DECOMPRESSION RATE 1 MIN/FT		
12325	ALL	REACH	20	O_2
12374	ALL	AT	20	AIR
12469	ALL	LEAVE	20	AIR
		REMARK: DECOMPRESSION RATE 1 MIN/FT		
12471	ALL	REACH	18	AIR
		REMARK: 5 HR 43 MIN HOLD AT 18 FT FOR EXPERIMENTS		
12813	ALL	AT	18	O_2
12814	ALL	LEAVE	18	O_2
		REMARK: SUBJECTS DESCEND TO 30 FT AT A RATE OF 3 FT/MIN WHILE BREATHING OXYGEN BY MASK		
12818	ALL	REACH	30	O_2
12834	ALL	LEAVE	30	O_2
		REMARK: DECOMPRESSION RATE 1 MIN/FT		
12854	ALL	REACH	10	O_2
12873	ALL	AT	10	AIR
12921	X	LEAVE	10	O_2
		REMARK: SUBJECT X IS MOVED TO ANOTHER CHAMBER WHERE HE BREATHES O_2 BY MASK AND DESCENDS TO 60 FT FOR TREATMENT OF DECOMPRESSION SICKNESS (KNEE PAIN)		
12925	X	REACH	60	O_2
12961	X	LEAVE	60	O_2
		REMARK: DECOMPRESSION RATE 5 FT/MIN		
12967	X	REACH	30	O_2
12968	X	AT	30	AIR
12972	X	AT	30	O_2
12997	X	LEAVE	30	O_2
		REMARK: DECOMPRESSION RATE 1 MIN/FT		
13017	X	REACH	10	AIR
		REMARK: X JOINING REST OF SUBJECTS TO CONTINUE DECOMPRESSION		
13047	ALL	LEAVE	10	O_2
		REMARK: COMPRESSION RATE 4 FT/MIN		
13052	ALL	REACH	30	O_2
13067	ALL	LEAVE	30	O_2
		REMARK: DECOMPRESSION RATE 2 MIN/FT		
13082	ALL	REACH	0	AIR

PREDICTIVE STUDIES IV

WORK CAPABILITY AND PHYSIOLOGICAL EFFECTS IN $He-O_2$ EXCURSIONS TO PRESSURES OF 400-800-1200 AND 1600 FEET OF SEA WATER

A COLLABORATIVE INVESTIGATION

EDITED BY
C.J. LAMBERTSEN, R. GELFAND AND J.M. CLARK



TECHNICAL EDITOR
M.E. FLETCHER

INSTITUTE FOR ENVIRONMENTAL MEDICINE
UNIVERSITY OF PENNSYLVANIA MEDICAL CENTER
PHILADELPHIA, PENNSYLVANIA

1978

F. PRACTICAL UNDERWATER WORK PERFORMANCE AT PRESSURES TO 1200 AND 1600 FSW

C.J. Lambertsen[1], K.M. Greene[1], R. Overlock[1] and J.M. Clark[1]

As part of the integrated physiological investigations of the Predictive Studies IV program, the effects of progressive rapid compression to 400-800-1200 and 1600 feet of sea water were explored (9).

At the time of this study, in 1975, repeated exposures of man had been conducted at rest and with various forms of physical exercise in the compressed helium atmosphere, but with little extension to determining capability for practical underwater work. The exercise accomplished in the "dry" chambers at high helium pressures had included arm and leg activity (7,11,13,14) and moderate-to-severe work with an ergometer bicycle (8,15). Studies of arm ergometer exercise had been conducted in subjects sitting submerged in water at pressures equivalent to 500 and 600 fsw (6). However, performance of practical forms of work underwater, even within experiment chambers, tended to be avoided at high pressure due to concern over its feasibility. These concerns related to influences of respiratory stress, CO_2 retention and neurological effects of compression. One study using underwater ergometer leg exercise was carried out in tests of breathing apparatus by the U.S. Navy Experimental Diving Unit in a water-filled plastic box surrounded by a helium-oxygen atmosphere at a pressure of 1600 fsw (16,17). It is surprising that, while studies to such

[1]Institute for Environmental Medicine, University of Pennsylvania.

high pressures in dry chambers and some nonworking ocean penetrations to 1148 fsw (2) were proceeding, a 1967 open-sea saturation diving trial to 615 feet, with working excursions to 636 fsw (12), remained the deepest demonstration of practical work performance at high pressure underwater (whether in laboratory chambers or in the sea) through the eight years to the time of this Predictive Studies IV.

The intent of the present program was to integrate specific physiological and performance investigations with a normal second step toward applying such observations. This step entails performing in a laboratory ocean simulator the degree and technical form of work ultimately to be carried out beneath the sea. Therefore, when it was learned that the subjects exposed to rapid excursion and saturation pressurization maintained physiological competence, the trials of practical work performance in water were carried out in a manner designed to simulate actual underwater work in diving.

It was evident that, with the lack of prior trials of work underwater at the pressures contemplated for Predictive Studies IV, no major base of experience existed to aid such trials.

Since the primary physiological investigative plan of purposely rapid excursions was to induce prominent effects of compression for study of onset and adaptation, until such detailed information was obtained in the dry helium environment it could not be certain whether the desired trials of practical work underwater would be sensible. However, to make provision for such trials it was necessary to establish in advance the conditions of work, to adapt breathing and safety systems, to accomplish technical and procedural training of subjects and investigators, and to make measurements of the respiratory and metabolic demands imposed by the planned underwater work functions. The preparations were accomplished prior to the beginning of rapid compression for the prolonged saturation-excursion studies of Phase II. Further training for the ultimate underwater work on excursion to the highest pressure of 1600 fsw was carried out at the stable elevated chamber pressure of 1200 fsw. Additional trials were performed at a helium pressure of 1350 feet during saturation-decompression.

METHODS

SUBJECTS AND CIRCUMSTANCES OF UNDERWATER WORK

The practical work task was accomplished by each of the four trained diver-subjects of Phase II (CC, GM, MP, FS). Figure 1 illustrates the general arrangement of chamber systems, subjects and the underwater work station used both for training and for the subsequent underwater work performance trials at the several levels of increased pressure. Since the diver-subjects worked in the chamber at a water depth of 10 to 12 feet, the underwater work trials were performed at pressures of 1210, 1360 and 1610 fsw.

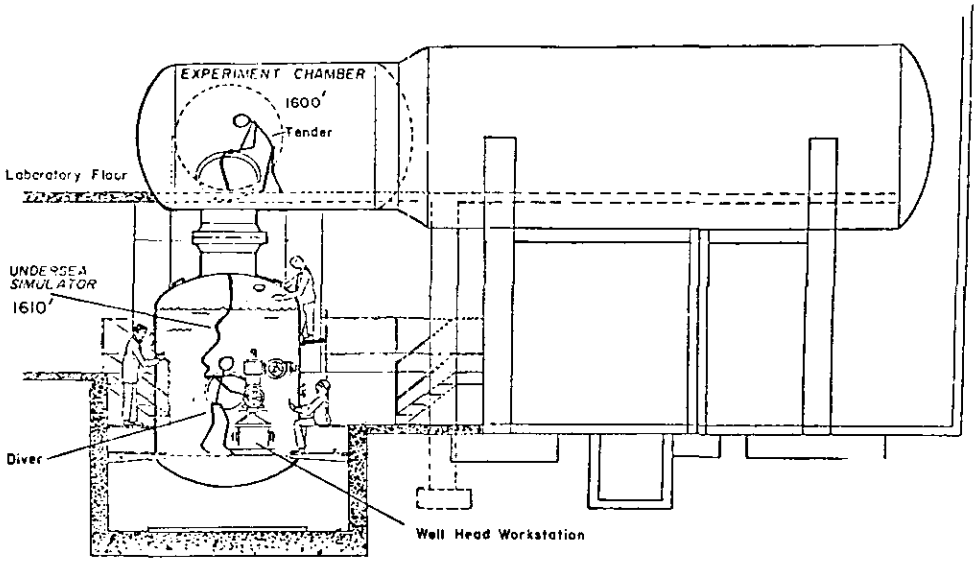


FIG. 1. Use of Water-filled Undersea Simulator Chamber System for Underwater Work Performance. Experiment Chamber pressurized with respirable helium-oxygen provides pressure on water surface of Undersea Simulator to simulate hydrostatic pressure in deep diving. Connecting Trunk is provided with stowable ladders.

The figure also indicates the positions of Tender and Diver-Subject relative to the Work Station during the underwater activity. The Diver-Subject and Tender compressed in a helium-oxygen atmosphere in the "Experiment Chamber" to the desired ambient pressure (e.g., equivalent to 1600 fsw). The Diver-Subject was secured by a harness, safety line,

gas hose and communication wire as he descended a stowable ladder into the water of the "Undersea Simulator," breathing helium with oxygen by mask. The timed sequence of tasks was carried out, following which the diver returned to the experiment chamber. Throughout the study the diver and tender were under continuous direct visual observation, as well as video and audio monitoring.

WORK STATION AND WORK SEQUENCE

An assembly of subsea oil wellhead components (Fig. 2) was designed (McEvoy Oilfield Equipment Company) and installed in the water-filled compartment of the undersea simulator system. The divers followed a prescribed and practiced routine of disassembly and reassembly of major

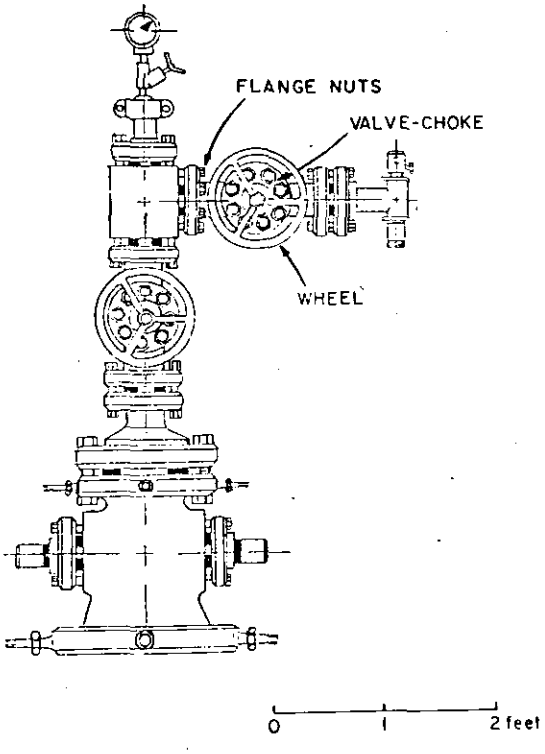


FIG. 2. Underwater Work Station. The assembly of high pressure fittings was devised by oil and diving industry engineers to provide appropriate task sequences for underwater work. Diver-subjects rigged, unbolted and removed valve-choke, then reassembled the system and removed the lifting rigging.

components, carrying out a timed sequence of work procedures lasting approximately ten minutes from start to finish. Table I shows the pattern of specific steps in disassembly and reassembly of the work station components. Tools employed included davit, winch, sling and wrench. Each diver-subject had accomplished at least five trials in

TABLE I. Pattern of Stages of Underwater Task Sequence. Percentages of Total Time Required to Perform Each Stage Are Based on Measurements Made at 10 fsw. (Mean Values From Four Subjects)

Task Stage	Components	% of Total Time
Rigging	Touch bottom Receive davit Assemble davit on well-head assembly Remove valve wheels Shackle hand winch ("come-along") to davit boom Rig wire cable winch sling to valve-choke body Apply tension with winch	18
Unfastening	Loosen valve-choke assembly nuts with wrench Remove all nuts to container	21
Disassembly-Reassembly	Remove valve-choke assembly Rig valve-choke assembly for surface lift Unrig for surface lift Replace valve-choke assembly Replace nuts, by hand	24
Torquing	Torque nuts with wrench	23
Completion	Release winch tension Remove sling Remove davit Rig davit for surface lift Replace valve wheels Finish	14
	Total	100%

water prior to excursion-saturation exposure and following training and practice in an air environment. The times required for completion of the task by each diver prior to pressurization are shown in Table II.

TABLE II. Times Required to Complete Underwater Work Task at 10 fsw

Subject			
CC	GM	MP	FS
10:20	9:59	10:07	8:37
11:00	11:06	11:37	9:36
11:10	12:08	11:48	10:14
15:08	12:55	11:53	11:37

Total times (min : sec) given for each subject are his four best attempts made during an initial trial sequence. These baseline values are compared with the subjects' performance at the high pressure circumstances in Table IV.

BREATHING APPARATUS

Helium with oxygen (1% O_2 at 1200 fsw, 2% O_2 at 1600 fsw) was the respired gas provided by open-circuit breathing systems which had been adapted to assure a sufficient free flow of gas at the highest ambient pressure utilized so that equipment-related resistance to inspiration would be avoided. Since the objective of the study was to determine human capability rather than equipment performance, it would have been undesirable to add apparatus resistance to the intrinsic pulmonary airway resistance associated with breathing helium at densities of 6.34, 7.24 and 8.92 g/l. It is well-recognized that superimposition of equipment resistance must limit ventilatory performance (16,17).

TEMPERATURE

Water temperature was maintained at 33°C (92°F) with no attempt to simulate the low water temperatures of the deep ocean since the intent was not to study temperature stress, but to determine whether hydrostatic influences would affect work ability. This design was further related to the awareness that means of heating divers in ocean water are now improving.

DEGREE OF WORK AND VENTILATORY RESPONSE

Respiratory minute volume was measured continuously during the practical work trials performed both in air and in the water-filled chamber at one ata pressure, using the breathing apparatus as part of the system for collecting the expired gas for volume measurement and analysis.

Repeated determinations of oxygen consumption were made in the four subjects during preliminary training in an air environment, the work chamber being empty of water. Figure 3 indicates the findings for the five task stages performed in air. Technical difficulties related to volumetric gas collection interfered with accuracy of initial measurements of ventilatory and metabolic cost of work underwater. For this reason one subject (FS) was studied repeatedly in air and in water following the Phase II saturation-excursion study, providing the necessary direct comparison of these conditions (Table III). From respiratory minute volume, inspired gas composition and continuous measurement of expired oxygen and carbon dioxide concentration, it was possible to derive a continuous indication of metabolic oxygen consumption and carbon dioxide production (Fig. 4). These measurements are used as indices of work pattern and degree of work for the standard task sequence employed at the increased ambient pressures.

TABLE III Ventilatory and Metabolic Costs of Work During Performance of Work Task Sequence in Air at 1 ata and in Chamber With Water Depth 10 fsw (Subject FS)

	Rest			0-2 min			2-4 min			4-6 min			6-8 min			8 - End		
	$\dot{V}_E$ (l/min BTPS)	$\dot{V}_{O_2}$ (l/min STPD)	$\dot{V}_{CO_2}$ (l/min STPD)	$\dot{V}_E$ (l/min BTPS)	$\dot{V}_{O_2}$ (l/min STPD)	$\dot{V}_{CO_2}$ (l/min STPD)	$\dot{V}_E$ (l/min BTPS)	$\dot{V}_{O_2}$ (l/min STPD)	$\dot{V}_{CO_2}$ (l/min STPD)	$\dot{V}_E$ (l/min BTPS)	$\dot{V}_{O_2}$ (l/min STPD)	$\dot{V}_{CO_2}$ (l/min STPD)	$\dot{V}_E$ (l/min BTPS)	$\dot{V}_{O_2}$ (l/min STPD)	$\dot{V}_{CO_2}$ (l/min STPD)	$\dot{V}_E$ (l/min BTPS)	$\dot{V}_{O_2}$ (l/min STPD)	$\dot{V}_{CO_2}$ (l/min STPD)
SUBJECT IN AIR AT 1 ATA																		
Trial 1	9.86	0.39	0.33	46.33	1.63	1.44	58.10	1.99	1.76	55.87	1.99	1.65	76.33	-	-	-		
2	8.78	0.34	0.29	50.64	1.65	1.46	60.95	1.93	1.67	66.82	1.99	1.76	80.35	2.45	2.23	-		
3	21.92	0.69	0.56	55.88	1.72	1.46	66.30	1.98	1.78	59.72	1.79	1.60	67.06	2.11	1.86	-		
Mean	13.29	0.47	0.39	50.95	1.67	1.45	61.78	1.97	1.74	60.80	1.92	1.67	74.58	-	-			
SUBJECT UNDERWATER 10 fsw																		
Trial 1	15.74	0.56	0.56	44.85	1.70	1.38	62.90	1.75	1.72	60.38	1.76	1.61	71.90	2.41	2.04	88.66	2.63	2.65
2	14.01	0.47	0.46	48.10	1.67	1.38	55.42	1.79	1.54	60.68	1.88	1.74	63.36	2.26	1.84	78.31	2.43	2.24
3	9.16	0.36	0.33	46.70	1.56	1.37	57.66	1.85	1.67	57.12	1.85	1.59	52.95	1.71	1.46	62.60	2.36	1.90
4	10.25	0.38	0.35	50.79	1.66	1.39	58.92	1.74	1.47	56.60	1.73	1.43	76.97	2.68	2.12	-	-	-
Mean	12.29	0.44	0.43	47.61	1.65	1.38	58.73	1.78	1.60	58.70	1.80	1.59	66.30	2.27	1.87	76.52	2.47	2.26

RESULTS

WORK AND VENTILATION

The metabolic and the ventilatory cost of performing the underwater task sequence (Figs. 3 and 4) were intentionally allowed to be greater than would have been appropriate for effective, sustainable practical work functions in actual open sea diving. Both in degree and in duration they much exceeded the underwater ergometer leg exercise more recently performed at 1400 fsw (3).

Ventilation reached approximately 60 liters per minute at the mid-point of the work period and increased further in the more strenuously paced activity involved in final reassembly of the work station components. The oxygen consumption averaged approximately 1.8 l/min at mid-point in subject FS and increased to 2.2 l/min in reassembly. These indices reflect not the task difficulty but the prominent degree and rate of exertion self-selected by the subjects to compete with their previous performance and task completion times.

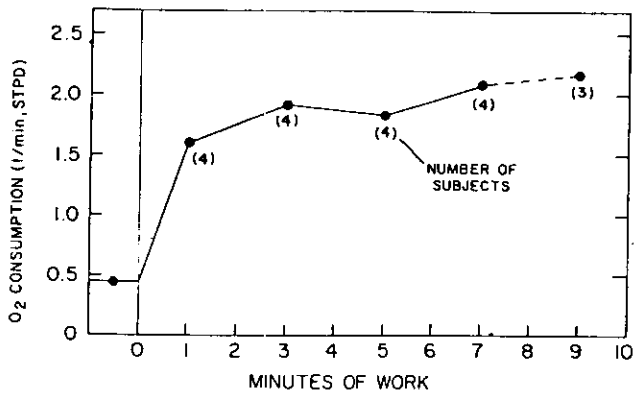


FIG. 3. Metabolic oxygen requirement of 2-minute periods in performance of underwater work sequence. Mean values of four subjects measured in air at 1 ata.

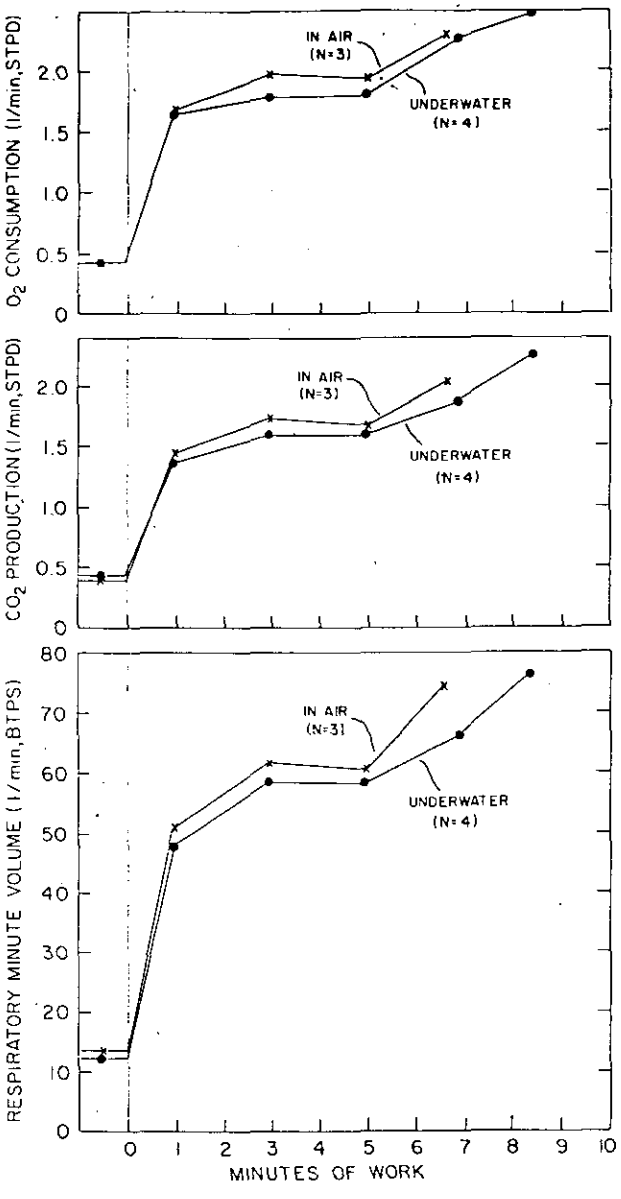


FIG. 4. Ventilatory and metabolic costs of work during performance of work task sequence. All measurements on subject FS: three trials in air at 1 ata and four trials underwater (10 fsw).

Metabolic rate was slightly diminished and time required for completion increased by work in water. Overall energy requirement was equivalent. Respiratory minute volume was slightly less in water than in air, matching the corresponding metabolic changes.

INFLUENCES OF WORK AND WATER

In Fig. 4 the effects of work in air and in water are shown to be not markedly different. The slightly lower oxygen consumption, carbon dioxide production and ventilation during work underwater evidently reflects the slightly lower rate of work imposed by adaptation to the water medium, and is consistent with the slightly longer time required to complete the total task sequence underwater.

PERFORMANCE AND TASK COMPLETION TIME

The specific work activities carried out in water by the Diver-Subjects included extensive movement and positioning of the body necessary to accomplish the tasks, fine finger activity and coordinated limb movement, skilled operation of the mechanical devices used to remove a heavy component, and the prominent exertion required for the self-paced overall task.

These specific performance functions, examined in shallow water by others (4), were photographically recorded here but not analyzed in detail. Table IV and Fig. 5 show the work duration required by each Subject-Diver to complete the total task sequence at each of the pressures used, from pre-compression to the excursion from 1200 fsw for underwater work at 1610 fsw. For each subject pair the first underwater work trial during the Phase II compression-pressure exposures was at a stable pressure of 1210 fsw, which represents essentially twice the prior "depth" for practical work underwater at increased pressures. In each case it followed the two successive daily excursion-compressions for detailed prior physiological measurements; this underwater work occurred on day 4 from the beginning of compression for each pair. It was therefore carried out in a period when considerable adaptation to the initial compression had been accomplished. No evident differences in symptomatic or objective responses to underwater work were observed between conditions of 1200 fsw and sea level.

The second underwater work sequence, performed on excursion from 1200 to 1610 fsw (Fig. 6), occurred for Subjects CC and GM on their compression day 5, and for Subjects GM and FS on their compression day 9. Except for controlled excitement at entering an entirely new situation, Subjects GM and FS

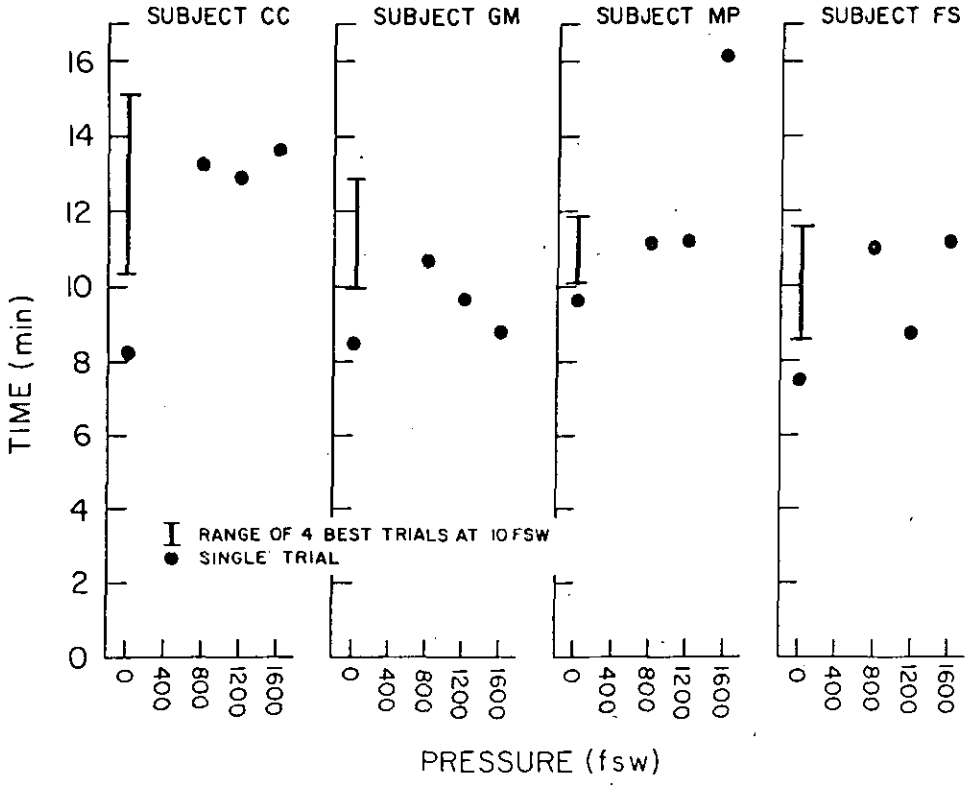


FIG. 5. Time for completion of underwater work task. Total times were generally not different at stable increased pressures compared with range of four trials at baseline condition of 10 fsw. Subject MP, however, had specific difficulty at 1610 fsw in aligning heavy valve flange with its stud fastenings.

experienced no unusual reactions and performed the practical underwater work and maneuvers in a manner equivalent to that demonstrated in water at 10 feet, under one atmosphere.

Immediately on compression from 1200 to 1600 fsw, subject CC felt an "anxiousness" and was allowed to conduct his underwater work on the same 55-minute excursion but following subject MP. Subject MP encountered a technical difficulty related to misalignment of the valve flange with the studs of the work station, which both extended his time (Table IV and Fig. 5) and led him to strive with greater than previous exertion before succeeding in reassembly and completing the task. Subject CC then proceeded with a smooth work performance.

TABLE IV Influence of Pressure and Conditions Upon Work Task Completion Time (time in min:sec). Underwater work at 10 fsw should be considered the baseline for comparison with the increased pressure states.

Condition	Subject			
	CC	GM	MP	FS
Air, 1 ata	8:16	8:30	9:40	7:31
Underwater, 10 fsw[a] (Pre-compression)	10:20-15:08	9:59-12:55	10:07-11:53	8:37-11:37
Underwater, 1210 fsw (at stable pressure)	13:14	10:45	11:10	11:02
Underwater, 1360 fsw (during saturation-decompression)	12:56	9:42	11:12	8:43
Underwater, 1610 fsw (during 1200-1600 fsw excursion)	13:40	8:48	16:09[b]	11:10

[a]Range of four best trials for each subject.

[b]Subject-diver MP encountered great difficulty when an unequal positioning of the winch sling interfered with the alignment of the flange holes of the heavy valve-choke assembly with the studs, grossly increasing work and duration.

FIG. 6. Subject-Diver performing task sequence at 1610 fsw pressure equivalent, on excursion from 1200 fsw.

The third underwater work sequence was performed at the 1360-fsw pressure during a stable phase of saturation-decompression, without excursion, to allow increased underwater working experience. No evident symptomatic or objective abnormalities occurred, and the work performance was generally equivalent to that at sea level.

BREATHHOLDING

As part of a general appraisal of respiratory control functions at increased ambient pressure, simple breathholding time was determined. Measurements were made without prior

hyperventilation, with inspired P_{O_2} of 0.2 atm, at 1200 fsw stable pressure and also over a range of ambient pressures during decompression with P_{O_2} of 0.5 atm. Breathholding ability was in all subjects found to be unaffected by ambient pressures from 200 to 1200 fsw. It was not measured during excursion to higher pressure. The normal breathholding function allowed the subjects at 1200 fsw to "breathhold dive" in the ocean simulator chamber to prepare equipment for the underwater work task performance.

DISCUSSION

It is the intention here to emphasize that, at both stable elevated pressures of 1210 fsw and on further excursion to the higher pressure of 1610 fsw, men were in fact capable of the respiratory, intellectual, technical and exceptional physical functions involved in performance of practical work underwater. For these Divers this represents success under physiological stress different from but at least equivalent to that of an Everest summit assault and clearly beyond the physiological stress of manned lunar exploration (10).

Since the experience with practical underwater work either in open sea or in chambers prior to this study was limited to a depth of about 636 fsw (12), these trials of underwater work at 1210, 1360 and 1610 fsw represent nearly a 1000-fsw increase in pressure for demonstrated practical working activity underwater. It is gratifying that these observations,along with background physiological investiga--tions of recent years,have already been extended to actual working exposures to 1500 fsw at sea (1).

While total experience is very limited, the demonstrated practicability in laboratory chambers and open sea makes it entirely likely that fine or gross practical work to the depths studied should be entirely feasible, once sufficient adaptation to initial pressurization has been accomplished. However, it must also be recognized that rapid compression to extreme pressures, such as those selected for the physiological studies which preceded these underwater work trials, can induce de-rangements which may be severe enough to temporarily completely preclude practical work in water or even in dry helium environment. Some symptoms of anxiousness and slight

tremor occurred in two subjects on rapid compression from 1200- to 1600-fsw pressure even after several days at 1200 fsw (Section E-1) and may have slightly affected the quality of work performance. Underwater trials on an earlier day might have generated a definite degree of interference with practical work. This is uncertain, but likely.

Clearly, in addition to duration of adaptation time, both the magnitude and rate of compression can be expected to determine the time course and completeness of the adaptations. These factors therefore should influence the delay required at a high pressure before effective and safe performance in water can be expected. This study has indicated that such delay falls within practical limits.

Following the practical demonstrations in this study and the physiological observations which led to them, it should be considered entirely feasible to carry out detailed investigation of underwater exercise and practical work. Studies of underwater ergometer exercise have recently been extended to stable pressures of 1000 fsw for arm activity (5), and 1400 fsw for leg work(3), and should be followed by investigation of other forms of work and other compression environments.

For the present, while continuing specific studies, it is important to recognize that skilled work has in fact been performed at 1610 fsw, and at sustained rates of physical exertion and ventilation greater than should ordinarily be necessary in the undersea circumstance simulated. In the performance of this underwater work the prominent dyspnea, reported in other investigations (3,17) in which subjects were continuously maintained at a stable 1400- or 1600-fsw pressure, was not encountered.

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Significance of the relationship between lung recoil and maximum expiratory flow[1]

JERE MEAD, JAMES M. TURNER, PETER T. MACKLEM, AND JOHN B. LITTLE
Department of Physiology, Harvard University School of Public Health, Boston, Massachusetts

MEAD, JERE, JAMES M. TURNER, PETER T. MACKLEM, AND JOHN B. LITTLE. *Significance of the relationship between lung recoil and maximum expiratory flow.* J. Appl. Physiol. 22(1): 95–108. 1967.—During forced expirations lateral pressures at points within airways equal pleural pressure, and the pressure drop from alveoli to these points approximates the static recoil pressure of the lungs. We regard maximum expiratory flow as set by this pressure and the flow-resistance of the airways upstream from these points. The resistance of these segments has a frictional component which increases as lung volume decreases and an accelerative component which decreases as lung volume decreases. The two components show systematic changes with age in normal subjects which are interpreted as reflecting differential loss of parenchymal and airway recoil.

mechanics of breathing; dynamics of airways; airway resistance; airway conductance; aging in lungs; flow-volume curves

IN THIS PAPER we develop a theoretical relationship between the static recoil of lungs and the maximum rate at which gas can be expelled from them. This relationship (the maximum flow-static recoil curve, MFSR) defines the resistance to gas flow offered by a particular segment of the bronchial tree, namely that running between the alveoli and points downstream where pressures at the inside wall of the airways equal pleural pressure. Changes in this resistance with changes in lung volume reflect the relative contributions of two components of the resistance: one, due to frictional losses, is small at high lung volumes and increases progressively as lung volume decreases; the other, due to convective acceleration of gas, mainly reflects the cross section of large airways and has its greatest effect at high lung volumes. We show that the relative magnitude of these components changes systematically with age in human subjects and we discuss the structural basis for these changes. We also relate our analysis to mechanisms limiting flow during forced expirations. We show that the configuration of maximum expiratory flow-volume curves, which we find to have greater detail than previously reported, can be accounted for by our theory. We begin by developing the central concept upon which our analysis is based.

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"EQUAL PRESSURE POINT" CONCEPT

Alveolar pressure, Palv, is the driving pressure which causes gas to flow through the airways. To a close approximation it exceeds the pleural pressure, Ppl, by an amount equal to the recoil pressure of the lungs, Pst(l). This may be expressed: Palv = Ppl + Pst(l). (Unless otherwise stated, all pressures are expressed relative to atmospheric.) Thus, the driving pressure may be thought of as being made up of two parts: one, Pst(l), is always positive in sign; the other, Ppl, is negative in sign for all inspirations and most expirations. During rapid expirations, however, it too is positive in sign. In this latter circumstance Palv is the sum of two components, Ppl and Pst(l), both of which are positive. Because Palv is the total pressure drop between the alveoli and atmosphere it follows that the pressure drop from the alveoli to some point within the airway must equal Pst(l). At this point the pressure at the inner wall must equal Ppl. The crux of our analysis is that we consider Pst(l) to be the driving pressure from the alveoli to this point, and Ppl to be the driving pressure from this point to atmosphere. We shall refer to the points where the pressure at the inner wall of the airways is equal to Ppl as equal pressure points (EPP).

What at first glance must seem an arbitrary division of a continuously changing pressure into two compartments becomes physically meaningful when we add the influence of pressure outside the airways. The pressure outside extrathoracic airways probably approximates atmospheric. The pressure outside intrathoracic but extrapulmonary airways—the trachea and the mainstem bronchi—is pleural pressure. The pressure outside pulmonary bronchi, which has generally been assumed to equal Ppl, has not been directly measured. Indirect measurements via neighboring blood vessels suggest that it may be systematically negative with respect to Ppl (12, 27).

Transmural pressure, Ptm, expresses pressure at the inside wall of a structure relative to that outside. Since, by definition, all pressures at inside walls upstream from EPP exceed Ppl, and since all pressures at outside walls are equal to or less than Ppl, it follows that all Ptm at points upstream from EPP are positive. All pressures at inside walls downstream from EPP must be less than Ppl. For extrathoracic airways Ptm downstream from EPP will be positive if inside pressures exceed atmospheric and negative if these pressures fall below atmospheric. For intrathoracic but extrapulmonary airways Ptm will be negative downstream from EPP. For intrapulmonary airways, if peribronchial pressures are negative with respect to Ppl, Ptm will be positive immediately downstream from EPP until points are reached where inside pressures have dropped by amounts equal to the difference between Ppl and peribronchial pressure. For points further downstream it will be negative.

From the foregoing it may be seen that EPP, whatever their location, divide the airways into upstream segments which have positive Ptm from downstream segments which may also have positive Ptm in portions of pulmonary and extrathoracic airways, but otherwise have negative Ptm. It follows that any compression of airways that occurs during forced expirations must take place downstream from EPP.

Location of EPP. While Ppl is subatmospheric there can be no EPP in airways—with the possible exception of the larynx where side pressures may be subatmospheric due to Bernoulli effects. Once Ppl increases to atmospheric, EPP are at the airway opening, and as Ppl increases still further they proceed upstream. How far do they go? We shall focus on events at the same lung volume so that the driving pressure for the segment upstream from EPP, namely the static recoil pressure, may be taken as constant. With driving pressure constant, flow through the upstream segment can increase only if the resistance of this segment decreases. One way for this to take place is for the EPP to move upstream, i.e., for the segment to shorten. We can assume, then, that EPP will continue to move upstream so long as flow increases. But it is well established that flow does not increase indefinitely as Ppl is increased. Isovolume pressure-flow curves (IVPF) introduced by Fry and co-workers (9) illustrate this. Some of these curves are presented in the following section (Figs. 1, 2, and 3). As Ppl increases flow increases with progressively smaller increments until a plateau is reached. With both flow and static recoil pressure fixed, the flow resistance of the upstream segment must be fixed and so must the location of EPP.

The sequence of events leading to fixation of EPP would be the following: When EPP reach the thoracic trachea a segment develops between the EPP and the thoracic outlet of the trachea in which Ptm is negative. For the intrathoracic trachea Ptm is zero at the EPP and, accordingly, all inside pressures downstream within the thorax are less than outside pressures. As Ppl increases and the EPP move upstream this compressed segment both lengthens and comes under a greater degree of compression. When the resistance of this compressed segment increases sufficiently rapidly with increasing Ppl to prevent further increase in flow, the EPP become fixed.

To summarize, at a given lung volume EPP appear first at the airway opening when Ppl is increased to atmospheric, move upstream along the airways, and become fixed when maximum flow is achieved. The fact that a plateau of flow is reached means that the EPP have progressed along intrathoracic airways to points when increases in compression of the intrathoracic airway downstream is sufficient to result in increases in downstream resistance which are directly proportional to Ppl.

Under conditions of maximal expiratory flow EPP divide the airways into upstream segments of fixed geometry (at a particular lung volume) and fixed driving pressure (Pst(l) at the volume in question) from downstream segments of variable geometry and variable driving pressure. Most of the remainder of this paper deals with the fixed segment upstream from EPP under conditions of maximal flow. Indeed, isolation of the comparatively simple events occurring in this segment from the more complicated ones downstream is the major purpose of the EPP concept. But first, we will use it to interpret isovolume pressure-flow curves in more detail.

Interpretation of IVPF curves in terms of the EPP concept. IVPF curves depict the relationship between pleural pressure and flow that exists at a particular lung volume. These curves were introduced by Fry et al. (8–10, 15) and used by them in a very fruitful way to analyze mechanisms limiting flow during forced expirations. We next show how these curves may be interpreted in terms of the EPP concept.

Just what IVPF curves are is most readily grasped by considering how they are obtained. To obtain them we estimated Ppl with esophageal balloons (25), volumes with a body plethysmograph (23), and flows with a pneumotachograph (6, 32). Subjects performed expired vital capacity maneuvers, slowly at first, and then more rapidly up to maximal levels. Volumes were expressed as percent of VC. Instantaneous values of esophageal pressure were plotted against simultaneous expiratory flows at the same lung volume—each vital capacity maneuver yielding one point at a given volume. Lines of best fit, as determined by inspection, were drawn through the points. Figure 1 shows a typical set of points and the curve based on them. Figure 2 shows an average curve at 65% VC based on measurements from eight healthy adult males.

We have pictured EPP as appearing at the airway opening as Ppl reaches atmospheric and moving upstream as Ppl exceeds atmospheric. Their arrival within the thoracic outlet should coincide with the onset of dynamic compression of the airways. We can gain some idea of the onset of dynamic compression by extending the flow-pressure relationship at low flows, where no dynamic compression has yet occurred, to higher flows, and noting at what point the experimental curve departs from this extension.

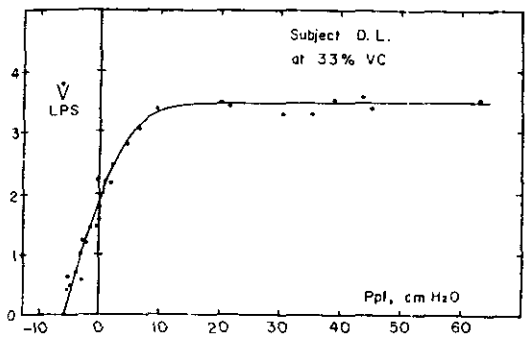

FIG. 1. Isovolume pressure-flow (IVPF) curve. The line was drawn by eye as the best fit to the points, each of which represents a separate expiration initiated from maximum inflation and measured at 33% VC.

The dashed line in Fig. 2 approximates the pressure-flow relationship that would obtain if no compression of the airways took place. It is based on an empirical expression $Palv = K_1 (V) + K_2 (\dot{V})^2$. This expression, which was introduced by Rohrer (30), has been shown to fit many pressure-flow relationships in the respiratory system. Curves were constructed which gave the best fit by eye to the experimental curves over a range of Ppl where no dynamic compression could take place, i.e., from $Ppl = -Pst(l)$ to $Ppl = 0$. The dashed line corresponds to the average values for K_1 and K_2 for these curves. Dynamic compression as indicated by the deviation of the solid from the dashed line becomes apparent when Ppl is some 12 cm H_2O above atmospheric.

Our theory predicts that Ppl at the onset of dynamic compression should equal the pressure inside the trachea at its thoracic outlet. We now make a separate estimate of this pressure. The side pressure at the thoracic outlet, Pto, is approximated by the following: $Pto = [K_a (\dot{V}) + K_b (\dot{V})^2] - K_c (\dot{V})^2$. The terms in the bracket describe the pressure loss due to frictional flow resistance from the thoracic outlet to the atmosphere. The remaining term represents the Bernouilli effect and is the gain in side pressure between the thoracic outlet and the atmosphere due to convective deceleration of gas. The line Pto in Fig. 2 is based on values for K_a, K_b, and K_c of 0.3, 0.4, and 0.1, respectively. The first two values approximate published data (5, 16). The value for K_c assumes a blunt flow profile (17) and a cross section at the thoracic outlet of approximately 2.5 cm^2.

The curve for Pto should intersect that for Ppl at the point where dynamic compression begins, and this is seen to be the case. To a certain extent this close correspondence is fortuitous since Pto is an approximation. That it is not simply a matter of chance is suggested by the equally good correspondence seen at a different lung volume. Figure 3 includes similar curves in the same subjects at 35% VC. Pto is markedly curvilinear and its intersection with Ppl occurs at a considerably smaller value than at the higher volume but, again, the intersection corresponds closely with the onset of dynamic compression.

APPENDIX I presents further analyses of the curves in Fig. 2 in terms of changes in resistance of the segments upstream and downstream from EPP, at a given volume, as Ppl is increased.

Significance of "negative effort dependence" in IVPF curves. The IVPF curves shown up to this point have true flow plateaus: beyond certain levels of Ppl flow remains nearly constant. In their original curves, Hyatt et al. (15) represented flow as decreasing from maximal levels as Ppl increased. It has since been shown (18) that this result is, at least in part, an artefact related to the use of a spirometer at the mouth to indicate isovolume conditions. During forced expirations the gas in the lungs is compressed and lung volume decreases progressively below that indicated by the spirometer. In this case, reductions in flow are to be expected since as lung volume decreases maximum flow also decreases.

With a body plethysmograph all volume changes, including those related to gas compression, are sensed and IVPF curves usually show definite flow plateaus. In 4 out of 18 normal subjects, however, we did observe decreases in flow from maximal levels. We shall refer to these as instances of "negative effort dependence" in the sense that flow decreased as effort increased.

The implication of negative effort dependence to the movement of EPP allows us to predict how much flow may be reduced. Driving pressure for the upstream segment being fixed, any decreases in flow imply increases in the resistance of the upstream segment, and, hence, movements of EPP in the downstream direction. Since EPP could not pass back beyond the thoracic outlet and still allow dynamic compression of intrathoracic airways, a lower limit for the flow reduction can be set: it should not be possible for flow to decrease below levels seen in the rising phase of flow when EPP first reach the thoracic outlet. In the example shown in Fig. 4, flow appears to approach this theoretical minimum. In none of the four subjects exhibiting negative effort dependence did flows decrease more than would be predicted on these grounds.

Volume range over which maximum flow is independent of effort. Before presenting our analysis of the resistance upstream from EPP we need to define the volume range over which truly "effort-independent" flow maxima occur. Hyatt et al. (15) initially estimated the effort-independent portion of the MEFV curves to begin between 30 and 50% VC. This estimate was later increased to 60% VC (13). From Fig. 2 it is clear that true flow plateaus occur at least up to volumes of 65% VC. We have made no attempt to see the maximum volumes at which plateaus could be achieved, but in five subjects they were demonstrated at levels of 70% VC or higher. From these results and from some additional experiments described in APPENDIX II, we have concluded that the effort-independent range of maximum flow extends at least to 70% of VC.

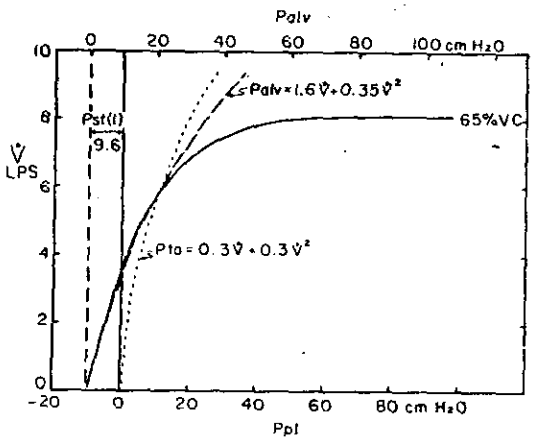

FIG. 2. Mean IVPF curve for six subjects at 65% VC.

ANALYSIS OF RESISTANCE OF THE UPSTREAM SEGMENT

To this point we have limited discussion to isovolume conditions. We now add *the dimension* of lung volume and restrict further analysis to the upstream segment.

Once maximum flow is achieved the resistance of the upstream segment at a given volume *is fixed and is the ratio of* Pst(l) to $\dot{V}_{max}$ at that volume. Since it is easy to obtain measurements of Pst(l) at any volume from static measurements (under static conditions Palv = *o and* Pst(l) = −Ppl) *and of corresponding* $\dot{V}_{max}$ from maximum expiratory flow volume (MEFV) curves, it is a relatively simple matter to describe how the resistance of the upstream segment *changes with lung volume*. In this section we prepare the way for interpreting such measurements.

The pressure drop along *the upstream segment* from alveoli to EPP will have two components: one, due to frictional losses from drag imparted by the airway walls and one due to convective acceleration of *the flowing* gas. (Hyatt and Wilcox (17) present a lucid account of convective acceleration and its significance in airway resistance.) The frictional component, Pfr, in turn, will have two components, *depending* on the nature of the gas flow. Where Reynold's numbers, Re, are less than 2,000, gas flow is probably laminar. Where they exceed 2,000, in particular if the passageways are irregular, gas flow is turbulent.

The pressure drop associated with each of these components depends on the geometry of the airways, the physical properties of the gas, and the magnitude of the flow. These are summarized in the following expressions:

$$Pla \sim \frac{L}{D^4} \times \mu \times \dot{V}$$

$$Ptu \sim \frac{L}{D^{4.75}} \times \mu^{0.25} \times \rho^{0.75} \times \dot{V}^{1.75}$$

$$Pca \sim \frac{1}{(D_{EPP})^4} \times \rho \times \dot{V}^2$$

Where la = laminar, tu = turbulent, ca = convective acceleration, L = length, D = diameters, μ = gas viscosity, and ρ = gas *density*.

The first expression is based on the Hagen-Poiseuille formula. The second expression combines the empirical formulations of Darcy and of *Blasius*.[2] The *third* expression is based on the Bernouilli formula. Here we are concerned only with the influence of geometry and flow. Corresponding expression for the three *components*, expressed *as resistances* and with the physical properties of the gas omitted are: Rla ~ L/D^4; Rtu ~ $(L/D^{4.75}) \times \dot{V}^{0.75}$; Rca ~ $(1/(D_{EPP})^4 \times \dot{V}$.

The total *pressure drop from* alveolus to EPP may be represented: Pst(l) = Pca + Pfr = Pca + Pla + Ptu. Similarly, the total resistance of the upstream segment may be represented as Rus = Rca + Rfr = Rca + Rla + Rtu.

Next, we predict how these components may be expected to change as lung volume changes. The *pertinent geometry for the* accelerative component is simply the cross section of the airways at EPP. If transmural pressures at EPP are zero, the cross section is that of the relaxed *tracheobronchial tree* and it should change with lung volume only to the extent that airway lengthening influences the relaxed cross section. Recent measurements of Hyatt *and Flath (14) suggest that in* the airways *of canine* lungs this influence is negligible. Since the points of fixation of EPP move upstream as lung volume decreases (see DISCUSSION) and since *transmural pressures for intrapulmonary* EPP may be positive, it is possible that the cross section at EPP actually increases with decreasing lung volume. On the other hand, if *transmural* pressures at EPP *remain* negligible even for intrapulmonary airways, their cross section should be largely independent of lung volume. This would be true because the total cross *section of the relaxed* tracheobronchial tree, of human lungs at least, remains nearly the same from the trachea to the level of bronchi of 2–3 mm internal diameter (30). We may *anticipate*, then, that *the cross section* at EPP under conditions of maximum flow should either remain unchanged or should increase as lung volume decreases. Since maximum flow *decreases with lung volume* and since the accelerative component of the resistance is flow dependent, we may predict that

[2] The following is Darcy's equation expressed in terms of pressure and flow:

$$P = \frac{F 16 L \dot{V}_D^2}{\pi^2 D^5 2g}$$

F is an empirical factor shown by Blasius to be approximated by the following for smooth-walled tubes:

$$F = \frac{0.316}{(Re)^{\frac{1}{4}}}$$

Reexpressed *in terms of* $\dot{V}$ is:

$$\frac{\dot{V}_D}{\pi D \mu}$$

Substituting Blasius' expression for F in Darcy's expression leads to the equation for Ptu in the text.

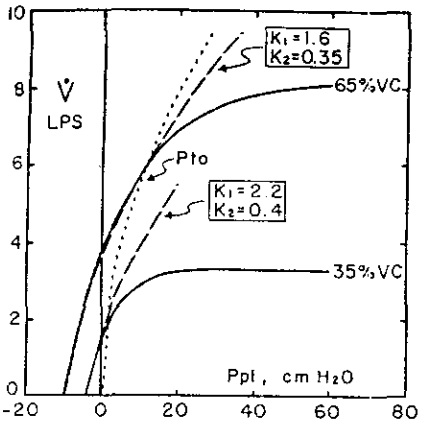

FIG. 3. Mean IVPF curves for six subjects at two lung volumes. The dashed line corresponds to line Palv and the dotted line to line Pto in Fig. 2.

the accelerative component of the resistance of the upstream segment will decrease as lung volume decreases.

The pertinent geometry for the frictional component includes the length and diameters of airways between EPP and alveoli. The length of this upstream segment will depend primarily on the position of the EPP at maximum flow and secondarily on the degree of extension of the tracheobronchial tree. As lung volume decreases all airways shorten and, furthermore, the fixation of EPP occurs at points progressively further upstream. Changes in diameter may be expected to have a greater influence on the resistance than changes in length. Over the volume range from 70 to 0% VC lung gas volume is reduced about 66% and airway diameters, which would be expected to vary approximately as the cube root of lung volume, would be reduced about 35%. The associated increase in resistance would be approximately sixfold. A 35% reduction in length, such as would occur if length and diameter changed equally, would decrease resistance by about one-third. The combined effect of reductions in length and diameter would then be approximately a fourfold increase in resistance. It seems doubtful that shortening of the upstream segment due to movements of the EPP at maximum flow would be so great as to reverse the tendency of the frictional component to increase as lung volume decreases. If we add now the influence of flow, we see that the frictional component would be unaffected by changes in flow if the flow is laminar, but would tend to decrease with lung volume if the flow is turbulent. Only in the instance of turbulent resistance would the geometric and flow effects be opposite.

Maximum flow-static recoil curves (MFSR)—Predicted configurations. The flow-pressure relationships of the upstream segment are represented by a graph of maximum expiratory flows against corresponding static recoil pressures. We will refer to these as MFSR curves. In Fig. 5 we show MFSR curves which would correspond to the predictions made in the last section if the components of upstream resistance existed in pure form. (The relationship between lung volume and Pst(l) is that of a young adult human lung.)

Figure 5*A* illustrates a purely accelerative resistance. The fine lines correspond to fixed cross sections at EPP. We have said that EPP move upstream as lung volume decreases and that cross sections at EPP may increase. The heavy line in Fig. 5*A* corresponds to this case. If the cross section at EPP remained fixed the MFSR curve would simply be one of the isocross-section lines.

Figure 5*B* illustrates a purely frictional resistance with laminar flow. The fine lines in this instance represent pressure-flow curves under conditions of constant lung volume. Here we assume resistance to be inversely proportional to volume expressed as percent VC. Accordingly, the slopes of the lines, which represent the reciprocal of resistance, namely, conductance, are directly proportional to volume. Pst(l) decreases with lung volume and the heavy line is the corresponding MFSR curve. It is seen to be curved in the opposite sense to that for a purely accelerative resistance.

Figure 5*C* corresponds to a purely frictional resistance but with turbulent flow. In this case pressure-flow curves at constant volume would be curvilinear. The curves are based on Rohrer's expression, $P = K_1(\dot{V}) + K_2(\dot{V})^2$. We assumed the ratio of K_1 to K_2 to equal 5, which is approximately true for the total airway. We also assumed K_1 and K_2 to be directly proportional to lung volume expressed as percent VC. The purpose of this example is not to give an accurate representation of the influence of turbulence but rather to show that the nonlinearity of pressure-flow curves which turbulence implies leads to a MFSR curve which combines the features of the purely accelerative and purely laminar frictional resistances. The MFSR curve would be curved in the same sense as for the laminar frictional resistance at low lung volumes but would tend toward the opposite curvature, namely, that seen for the purely accelerative resistance at high volumes.

To the extent that the accelerative or turbulent frictional resistance is important, we may expect that MFSR curves will be curvilinear in the sense shown in Fig. 5*A* and in the upper portion of Fig. 5*C*. To the extent that frictional resistance is important, we may expect curvature in the opposite sense at low volumes. It is also clear that an appropriate combination of these components might result in MFSR curves which would be nearly linear, in which case the resistance of the upstream segment would be substantially independent of lung volume.

MAXIMUM FLOW-STATIC RECOIL CURVES IN MAN

In conjunction with a study of changes in static recoil of lungs with age in man, we obtained MEFV curves as well in an effort to relate individual differences in static recoil pressure to maximum flows. When we later developed the ideas presented here, we had data for about

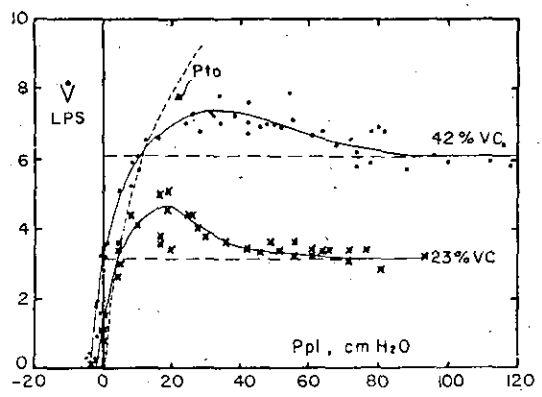

FIG. 4. *VPF curves at two lung volumes in a subject who exhibited reductions from maximum flow with increased expiratory effort. The individual points correspond to separate expirations, each begun from maximal inflation. Note that with increasing efforts, flows decrease to levels which correspond to ones that would obtain for EPP located near the thoracic outlet.*

40 subjects ranging in age from 13 to 64 with which to describe the pressure-flow characteristics of the upstream segment.

The static recoil curves were obtained by the method described by Milic-Emili et al. (25). All measurements were made in the upright posture. *Before each determination* the subject inspired maximally three times in order *to assure* a constant volume history. He then inspired maximally and breathed out slowly into a spirometer. The tubes to the spirometer were occluded by means of a clamp at fixed volume increments—usually at 80, 60, 40, 20, 10, and 0% VC. Static transpulmonary pressure was measured as the difference *between mouth and* esophageal pressure during the periods of occlusion. *Curves were constructed* from mean values from at least three separate maneuvers.[3]

For the MEFV curves, subjects, seated in a body plethysmograph, inspired maximally three times and then breathed out as rapidly as possible from the maximal inspiratory level (TLC) to the maximal expiratory level (RV) through a calibrated flowmeter of either the Silverman (32) or Fleisch (6) type. Separate determinations of TLC were measured in all subjects by the method of DuBois et al. (4).

Figure 6 shows four typical sets of curves. Figures 7 and 9 include additional examples of MFSR curves. All MFSR curves were curvilinear in the sense *predicted for* accelerative resistance and/or turbulent frictional resistance *at high lung volumes*, and in the sense predicted for

[3] *Particularly* in younger individuals, esophageal pressures deviate in the positive direction at low lung volumes (25). We have assumed these deviations to be artefactual and have drawn straight *lines from points estimated* by inspection to be free of such artefacts (usually about 30–40% VC) through zero pressure at RV in order to approximate Pst(l) at intermediate volumes. These interpolations probably *somewhat underestimate Pst(l).*

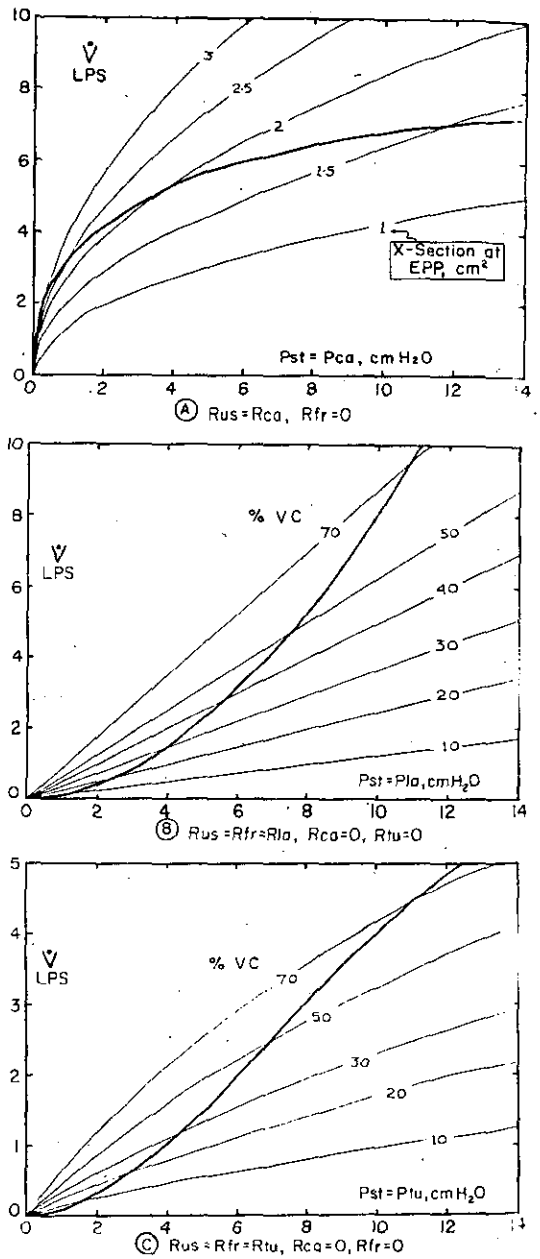

FIG. 5. Theoretical flow-pressure curves for the segment upstream from EPP. *A:* for purely accelerative resistance, *B:* for purely laminar frictional resistance, *C:* for purely turbulent frictional resistance.

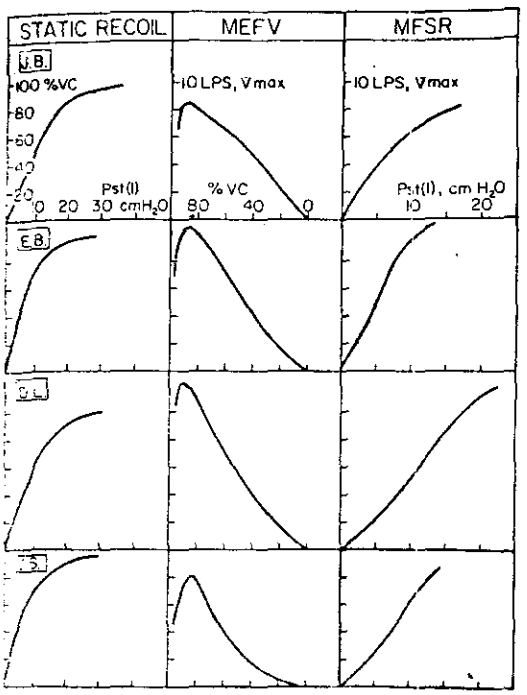

FIG. 6. Static recoil, maximum expiratory flow-volume (MEFV), and maximum flow-static recoil (MFSR) curves for four healthy male subjects.

frictional resistance at low lung volumes. In some instances the curves were nearly linear.

Estimates of the cross section of major airways from MFSR curves. We have attempted to assess the relative importance of accelerative and frictional components of resistance of the upstream segment at high lung volumes along the following lines. If convective acceleration accounts for most of the pressure drop in the upstream segment at high lung volumes, it should be possible to estimate the cross section at EPP from MFSR curves. We have done this and compared such values with separate estimates based on measurements made on X-ray films. Although peak flow is probably effort dependent, its relative insensitivity to changes in external resistance (see APPENDIX II) suggests that dynamic compression has at least begun and that EPP have reached the intrathoracic trachea. On the other hand, Macklem and Wilson (20) have demonstrated that EPP at high lung volumes under conditions of truly effort-independent maxima do not proceed further than the lobar bronchi. This places EPP at peak flow somewhere between the thoracic outlet of the trachea and the lobar bronchi. Estimates of the cross section of these airways can be made from chest X-rays and the fact that the relaxed total cross section of the airways is similar for the first few generations (30).

Figure 7 illustrates how we used the pressure-flow relationships to make our estimates. The dashed lines are isopleths corresponding to known cross sections. The experimental curves tend toward the configuration of the isopleths at high lung volumes, i.e., at high Pst(l). We made visual estimates of the isopleths which most nearly corresponded to the experimental curves for 16 subjects. We also obtained posteroanterior (PA) and lateral chest films on these 16 subjects and measured the transverse and PA diameters of the shadows of tracheal gas in the immediate vicinity of the carina. The lateral films were slightly underexposed and the PA films overexposed, compared to usual chest X-ray technique, to best visualize the tracheal air shadow; in about one-half of the subjects, one or two additional films were required before satisfactory contrast was obtained. In one subject, one of the diameters could not be discerned and it was assumed that the diameter measured at a different level was the same. All films were exposed at RV so that transmural pressures were as near zero as possible. Corrections were applied to the measured diameters for magnification of the image due to the relative distances of the trachea and X-ray tube from the film. Cross-sectional areas were then calculated based on the assumption that the cross section was elliptical.

The results are presented in Fig. 8. On the average, the cross section at the EPP estimated from MFSR curves exceeded that of the trachea at the level of the carina as estimated by X-ray measurements by 16%. We have concluded from these measurements that at high lung volumes convective accelerative losses account for almost all of the flow resistance of the segment upstream from EPP.

MFSR curves in normal subjects of different ages. The 40 subjects for whom we had MFSR curves included 5 males under 20 and 5 over 45 years of age. Two additional age groups of 5 subjects each were selected from the remainder on the basis of lung size as judged by measurements of total lung capacity (TLC). In this selection we attempted to make the differences in average TLC among the groups as small as possible. Figure 9 presents the individual MFSR curves of the 20 subjects. From inspection there appear to be systematic changes with age in the configuration of MFSR curves. Figure 10 presents average static recoil, MEFV and MFSR curves for the four age groups. Volumes are expressed as percent TLC so that differences in residual volume, RV, may be shown. Flows are expressed in TLC per second rather than in LPS in order to adjust for differences in body (and, hence, lung) size.

Static recoil pressures at a given volume decrease markedly from the youngest to the next youngest group but without associated change in RV. The next older group exhibits further reduction in Pst(l) bus with an increase in RV. The oldest group shows no further reduction in Pst(l) but RV is increased.

Peak flows did not differ significantly between the groups but maximum flows appeared to fall off more rapidly with decreasing lung volume in the older subjects—resulting in increased curvilinearity of MEFV

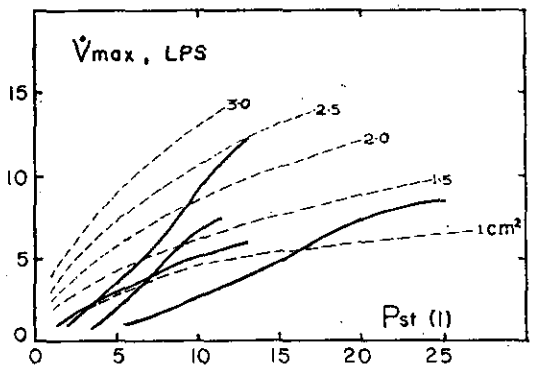

FIG. 7. Typical MFSR curves (solid lines) together with pressure-flow curves for accelerative resistance (dashed lines) corresponding to the cross sections at EPP as indicated. Note that the experimental curves appear to conform to the *theoretical* curves in their upper portions.

curves which became increasingly convex to the volume axis.

The flow resistance of the upstream segment is the ratio of *Pst(l) to the corresponding* $\dot{V}_{max}$. Average values for the different age groups are plotted against lung volume in Fig. 11 together with similar graphs for conductance of the upstream segment. (Conductance, G, is the reciprocal of resistance.) The latter is the more striking representation inasmuch as it reveals a nearly linear dependence of conductance at low lung volumes which extends progressively to higher volumes in the older subjects. At high lung volumes older subjects have higher conductances than younger ones. As lung volume decreases this relationship reverses.

We offer the following interpretation of these changes: Aging is accompanied by diminished elastic recoil of *lungs resulting in decreased static recoil pressure* at a given lung volume. It probably also is accompanied by increases in the resting length of virtually all elastic structures, including the walls of airways. With increasing age the relaxed cross section of airways increases while Pst(l) decreases. The time course of these opposing influences is such that $\dot{V}_{max}$ at high lung volumes shows little change.

At low lung volumes, where frictional resistance of the upstream segment dominates, the airways responsible for the resistance of the *upstream segment are subjected* to transmural pressures tending to expand them in proportion to Pst(l). Whether these airways increase or decrease in cross section with age depends on the balance of changes in elastic recoil between the airways and pulmonary parenchyma. For example, it is easy to picture a combination of diminished airway and parenchymal recoil which would result in no change in airway cross section at a given lung volume. One possible interpretation of the increase in resistance of the upstream segment with age at low lung volumes is that *parenchymal recoil* decreases with age more rapidly than airway recoil. This would result in a diminished cross section of airways at a given volume, and an increase in resistance of the upstream segment at low volumes.

The finding that conductance of the upstream segment decreases nearly linearly with lung volume in older subjects and appears to extrapolate to zero near RV suggests that airways upstream from EPP must approach total collapse at RV and that RV is set by properties of the lungs rather than of the chest wall in such individuals. Leith and Mead (unpublished observations) have obtained experimental evidence for this. They found that older normal subjects performing the VC maneuver remain on their MEFV curves as long as they continue their attempts to expire. In contrast, many young subjects remain on MEFV curves only transiently. In these, recoil of the chest wall appears to attenuate Ppl sufficiently to reduce it below levels needed to produce maximum flow. In the last portion of the VC in these individuals flow becomes effort dependent.

DISCUSSION

Direct observations of the location of EPP. Macklem and Wilson (20), by measuring lateral intrabronchial pressure in human subjects, have confirmed the theory of the development and movement of EPP during the course of an isovolume pressure-flow curve. Their diagrams show that EPP develop in the intrathoracic trachea when the pleural pressure has become sufficiently positive to overcome upper airway resistance, that they move upstream with increasing flow, and that they probably become fixed at $\dot{V}_{max}$. Over the middle half of the VC *it was* estimated that EPP stopped moving just beyond the level of the lobar bronchi. Below 25% VC it was thought *that EPP moved further upstream.* Pride and Nadel (unpublished observations) have shown in living cats that EPP are at the level of the lobar bronchi at peak

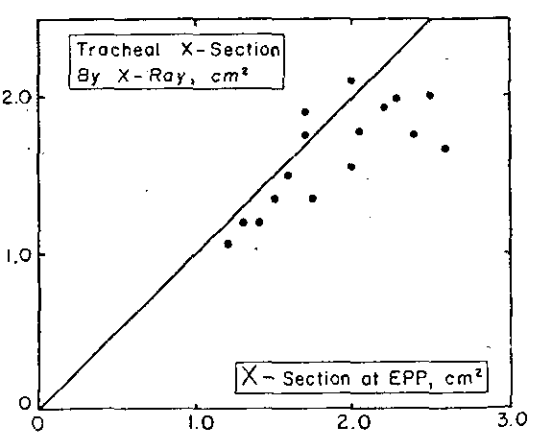

FIG. 8. Cross sections of the trachea estimated from chest films taken at residual volume *plotted against cross sections at EPP* estimated from MFSR curves.

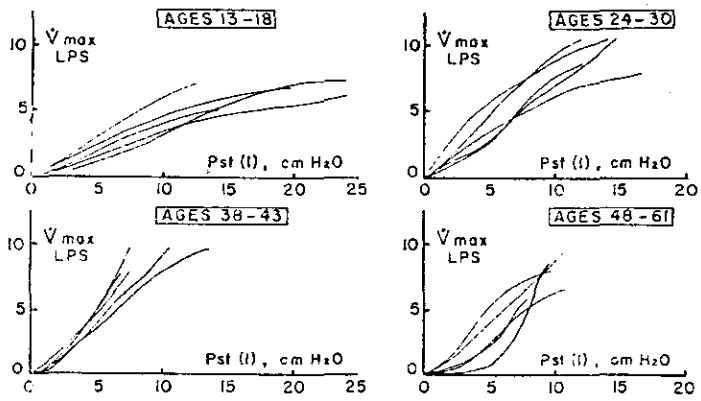

FIG. 9. MFSR curves for 20 subjects arranged in four age groups.

flow. Subsequently, Macklem and Mead (unpublished observations) have measured the location of EPP in living dogs. Their measurements confirm that at $\dot{V}_{max}$ EPP stop moving and stay at the same location despite further increases in Ppl. At high lung volumes the EPP were generally at the level of the lobar bronchi and moved upstream slightly as volume decreased to 40% of VC. Below 40% of VC, EPP moved upstream markedly. They also found retrograde movement of EPP in association with negative pressure dependence of flow in excised lungs.

Comparison of forced and relaxed expirations. Pierce (29) and also McIlroy et al. (22) have called attention to the fact that the time course for forced expirations is similar to that for relaxed expirations. McIlroy et al. pointed out that in both instances flow decreases nearly linearly with volume and the slopes of volume-flow plots are similar. These slopes have the units of time and approximate the mechanical time constants of the system. (The equation of motion of the passively expiring respiratory system is $V/C + RV = 0$ which, rearranged to $V/\dot{V} = -RC$, defines the slope of the volume-flow relationship.) The observation that forced expirations appear to have time constants similar to those for relaxed expirations suggests the possibility of a similar mechanism. Our analysis leads to this conclusion. In the case of forced expirations the pertinent compliance is that of the lungs and the pertinent resistance that of the upstream segment which, in young individuals, is seen to be relatively independent of lung volume. The compliance of lungs is approximately twice that of the lungs and chest wall and the resistance of the upstream segment is about one-half that of the total respiratory system. Similar time constants for relaxed and forced expirations are to be expected on this basis.

Configuration of MEFV curves. Since their introduction by Hyatt et al. most analysis of MEFV curves has been focused on their lower portions. We find that the effort-independent part extends to higher volumes than has been generally recognized, and that this more extensive curve has three distinct segments: an uppermost one convex to the volume axis, a midportion concave to the volume axis, and a lowermost portion convex to the volume axis. According to our analysis the uppermost curvature reflects the curvilinearity of the static recoil curve at high lung volumes: Pst(l), the driving pressure for the upstream segment, falls off rapidly as lung volume decreases from high levels, and the reduction in flow reflects this. Indeed, if the resistance of the upstream segment were constant, MEFV curves would have precisely the same configuration as static recoil curves. The departures from such a configuration reflect at higher volumes the contribution of accelerative and turbulent frictional resistances, which tend to decrease with lung volume and, at low volumes, the frictional resistance of the upstream segment which increases with further decrease in lung volume.

The factors determining flow throughout the entirety of the forced expiratory vital capacity may be summarized as follows: in the rising phase of flow the driving pressure depends on the force developed by the expiratory muscles which, in turn, depends on their speed of contraction and velocity of shortening (1). This driving pressure is opposed by the total flow resistance of the respiratory system including the entire airway as well as that of the tissues of the lung and chest wall and any resistance of the measuring equipment. As flow rises EPP move rapidly upstream along the airways and become fixed at points in the neighborhood of the lobar bronchi. In normal individuals this occurs by the time 25–30% of the vital capacity has been expired. Beyond this point flow is independent of muscular effort as long as the effort is above certain levels. Flow may then be thought of as being determined by the static recoil pressure of the lung and the flow resistance of the airways between the alveoli and EPP. As we have stated, initially, that is at high lung volumes, this resistance is almost entirely accelerative, but as flow falls off and volume decreases the frictional resistance of the segment predominates. Finally, at least in young individuals, the rising opposition of the chest wall to further volume change opposes the falling static recoil of the lungs suffi-

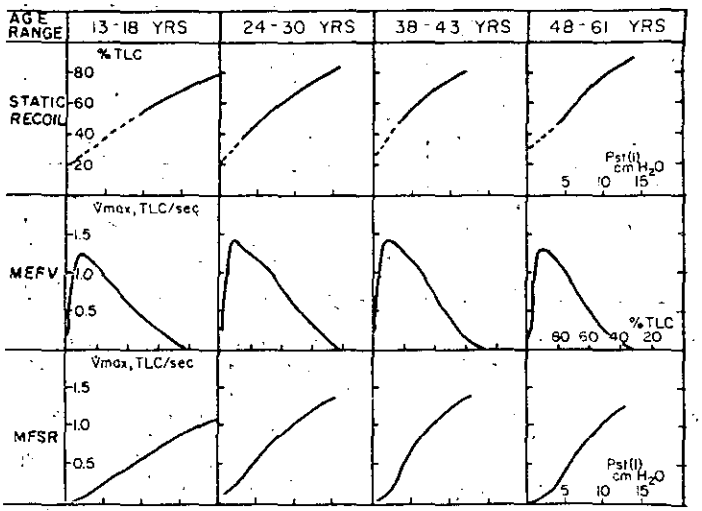

FIG. 10. Mean static recoil, MEFV, and MFSR curves for 20 normal subjects arranged *in four age groups of* 5 subjects each. The broken lines in the static-recoil curves are interpolated.[3] Maximum flows were divided by individual total lung capacities and expressed *in TLC's per second* to adjust for differences in lung size.

ciently to allow the EPP to move back up the tracheobronchial tree, and during the very last portion of the maneuver flow is again determined by effort.

When maximum expiratory efforts are initiated at TLC peak flows are attained at high lung volumes. These are commonly thought to be more effort dependent than maximum flows at lower volumes. But if EPP reach intrathoracic airways, which is probably the case in almost all instances, peak flows may be thought of as being limited by the cross section of the major airways and the static recoil of the lungs. When airway resistance is high, the *frictional component of the resistance* upstream from EPP must be appreciable even at high lung volumes and, in this case, peak flows would be sensitive to frictional resistances as well.

Application of the EPP concept to abnormal lungs. In our analysis we have treated the lungs as a unit. This approximation loses some of its usefulness in diseased lungs where nonuniformity may become the dominant feature. When this is the case some pathways will empty faster than others. These rapid compartments will contribute more to the MEFV curve *early in the expiration—that* is, at high lung volumes, whereas the flows obtained at lower volumes will be more influenced by the emptying *rates of the slower* units. Turner and Mead (unpublished observations) have shown that this is an additional cause for convexity toward the volume axis of the MEFV curve. In addition, they have predicted that when nonuniformities occur maximum expiratory flows should exhibit "time dependence" as well as volume dependence. That is, they predicted that the value of $\dot{V}_{max}$ at any given lung volume would depend in part on the time taken to arrive at that particular volume. They have obtained experimental evidence of such time dependence, both in *older normal subjects and in patients* with obstructive lung disease. Tests of ventilatory capacity in such instances may be more influenced by this additional dimension than they are by the factors listed in the previous section.

Comparison with other theories of maximum expiratory flow. Fry (8) was the first to attempt a rigorous explanation of the mechanisms limiting expiratory flow. He has applied aerodynamic theory to events occurring along the whole *airway and has developed the concept of the "flow-limiting segments."* These segments were the first to narrow sufficiently to limit flow. Analysis is complicated due to the difficulties in accurately characterizing events occurring along the whole compressed segment.

Permutt and co-workers (26) have made extensive and valuable use of a simple mechanical analogue, the Starling resistor, to explain the dynamics of flow through collapsible tubes. They point out that when the pressure at the outlet of the tube is less than the pressure surrounding it, flow becomes dependent *on the difference between* driving and surrounding pressure and independent of the difference between driving and outlet pressure. In applying these concepts to the lungs, it is seen that surrounding pressure is Ppl, driving pressure is Palv, and outlet pressure is atmospheric. Once $\dot{V}_{max}$ is reached we have shown that flow is dependent on the difference between driving and surrounding pressure, i.e., Pst(l) and independent of the total pressure drop from alveolus to atmosphere. This is closely analogous to the behavior of the Starling resistor. The major difference between *it and* the lung is that in the latter at any given volume, flow continues to increase even though Ppl rises considerably *above atmospheric.* As discussed previously, this is in part due to the pressure required to move EPP to the thoracic outlet and in part because a finite pressure is required to increase the resistance of the compressed seg-

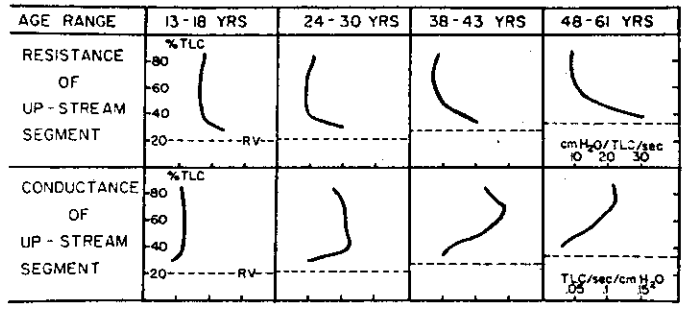

FIG. 11. Average relationships between resistance or conductance of the upstream segment and lung volume in the four age groups.

ment sufficiently to limit flow. It is in attempting to explain these differences that our concepts diverge from Permutt's.

Permutt (personal communication) suggests that, at a given volume, flow continues to increase until the transmural pressure across the wall at some point along the airway reaches a critical value Ptm', which is sufficient to limit flow. Ptm' is equal to the transmural pressure required to close the airway under static conditions when no air is flowing. He states that all events downstream from Ptm' would be irrelevant and have no effect on flow. This permits him to restrict his analysis only to the segment upstream from Ptm' which he regards as a fixed resistor with a fixed driving pressure. Although this approach avoids the complexities of analyzing the variables with which Fry must contend, it still requires consideration of events in the compressed segment. In the normal lung, at least, the pressure required to close the airway, Ptm', must lie downstream from EPP.

Our concepts, which make no attempt to explain the exact mechanisms by which flow is limited and, therefore, in no way conflict with the views of Fry or Permutt, ignore the compressed segment and thereby simplify the analysis still further. We have divided the lungs into two separate physical parts which are in series. The analysis of one part is complicated (downstream from EPP) but the analysis of the other (upstream from EPP) is straightforward. Because they are in series, flow through the whole system may be described if we know the factors governing flow through either of the parts. The factors governing flow through the upstream segment (i.e., Pst(l) and the resistance of small airways) are parameters long known to be important in pulmonary mechanics and easily measured. Although elastic recoil has been recognized to be a factor governing maximum flow its role has been thought to be indirect through its influence on airway caliber (2). We assign it a direct role in which it is the driving pressure-producing flow through the upstream segment. Similarly we assign a direct role to the upstream conductance so that $\dot{V}_{max}$ is directly proportional to both of these parameters.

Furthermore, pathophysiological changes occurring with disease primarily affect the upstream segment. Reductions in $\dot{V}_{max}$ are directly proportional to reductions in both the pressure due to elastic recoil and the conductance of the smaller airways. As either of these parameters approaches zero, $\dot{V}_{max}$ also, approaches zero. Changes in the downstream segment, in which an increase in compressibility is the only clinically relevent example, will have a much more limited influence on $\dot{V}_{max}$. The extreme instance would be a trachea so collapsible that flow limitation took place as soon as EPP reached the thoracic outlet. $\dot{V}_{max}$ would then be that observed at the crossover of curves Pto and P in Figs. 2 and 3. Increased collapsibility at any other level could have only a smaller, not greater, effect. We conclude that changes upstream from the flow-limiting segment account for most of the limitation of expiratory flow seen in pulmonary disease. We also conclude that surgical intervention with the aim of rendering the walls of the airways more rigid can result in only a limited increase in $\dot{V}_{max}$ (11).

Relevance of the EPP concept to the cough mechanism. In healthy individuals the only circumstance in which the mechanisms discussed in this article come into play naturally is during coughing; thus their principal pertinence is to expectoration rather than ventilation. Dynamic compression of the intrathoracic airways is undoubtedly an essential part of an effective cough since it makes possible the high kinetic energy of the air stream required to move material at the airway wall (3, 20, 31, 33). It is possible that instability leading to rapid oscillations of the wall serve to concentrate the energy further but, whatever the precise nature of the mechanism, it is apparent that a cough would be largely ineffective in airways that did not undergo compression. Seen from this point of view, the position of EPP takes on added significance: cough is only effective at points downstream from them. In healthy individuals, EPP are in relatively large airways at high lung volumes and move upstream as lung volume decreases. In these, the cough should be effective at different levels of the tracheobronchial tree depending on the lung volume at which the cough is produced. A series of coughs without intervening inspirations would tend to clear progressively "deeper" portions of the airways.

It is probably true that an effective cough is an important homeostatic mechanism and that abnormalities

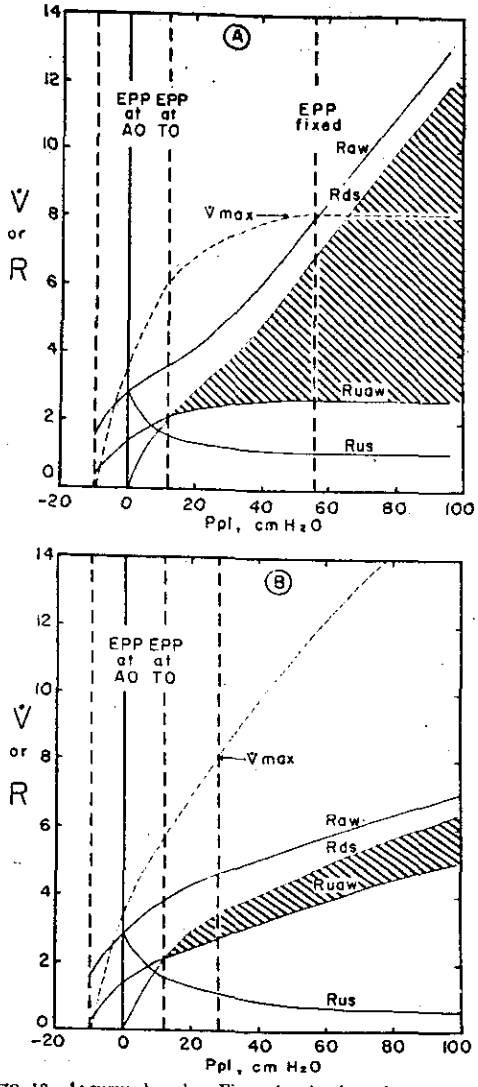

FIG. 12. *A:* curves based on Fig. 2 showing how the resistance of the total airway, Raw, and of three segments: the upper airway, Ruaw, the segment downstream from EPP, Rds, and that upstream from EPP, Rus, change as Ppl increases. The solid lines are resistances and are in cm H_2O/LPS and the broken line indicates airflows in LPS. *B:* partitioning of airway resistance for incompressible airways.

of this mechanism predispose to pulmonary disease. The interesting feature of our theory from this standpoint is that changes in airways which might profoundly influence the cough mechanism could well have an undetectable influence on ventilatory performance. This statement is a corollary of our earlier conclusion that increased collapsibility of airways per se would be expected to have comparatively little influence on maximum flow, but this same increase in collapsibility would profoundly effect movements of EPP and, hence, the extent of dynamic compression. For example, abnormally high compliance of major airways could render coughs totally ineffective for all intrapulmonary airways and, at the same time, have only a modest influence on maximum flow. These abnormalities have been described in patients with bronchiectasis (9) and in patients with bronchitis and emphysema (19). In the former group, indeed, ventilatory performance is usually well maintained but bronchial pressure measurements and bronchography during coughing and forced expiration revealed that bronchiectatic sacs generally underwent no compression and the pressures within them remained high due to the collapse of lobar bronchi (7). The patients with bronchitis and emphysema also had collapsing lobar bronchi during forced expiration which, in some patients, prevented compression of airways upstream over the whole vital capacity. In these patients EPP presumably never went beyond the lobar bronchi, rendering cough almost totally ineffective in ridding the smaller airways of their secretions (19).

APPENDIX I

Use of isovolume pressure-flow (IVPF) curves to partition airway resistance. In this appendix we use IVPF curves to partition changes in airway resistance between the segments upstream and downstream from EPP. The driving pressure from alveolus to atmosphere, Palv, is approximated by Ppl + Pst(l), which is seen in the example of Fig. 2 to equal the horizontal distance between the ordinate at Ppl = −9.6 cm H_2O and the experimental curve. The driving pressure for the upstream segment is Pst(l) which, in this instance, is 9.6 cm H_2O; that for the downstream segment is Ppl which is the horizontal distance between the ordinate at Ppl = 0 and the experimental curve. The driving pressure from the thoracic outlet of the trachea to the atmosphere, i.e., for the extrathoracic or upper airways, is the horizontal distance from the line Pto to the ordinate at Ppl = 0.

The resistance of the airways and their various segments is expressed as the ratio of corresponding driving pressures to flow, flow being the same for all segments. Figure 12*A* shows total airway resistance, Raw, upper airway resistance, Ruaw, and the resistances upstream and downstream from EPP, Rus and Rds, respectively, all plotted against Ppl. Resistances upstream and downstream from EPP are defined only for Ppl greater to or equal to 0.

Figure 12*B* shows these resistances for rigid airways and is based on the dashed line in Fig. 2. It is shown to clarify the contribution of dynamic compression.

The two representations are identical until EPP reach the thoracic outlet of the trachea. Thereafter, Raw increases more in Fig. 12*A* than in Fig. 12*B* due to compression of the segment between the EPP and the thoracic outlet. Indeed, a point is reached beyond which Raw and Rds increase in direct proportion to their driving pressures; from that point on, flow remains fixed and independent of further increases in Ppl. With flow fixed the EPP have reached their furthermost points upstream.

By comparing Fig. 12*A* and *B* we gain some idea as to the extent of dynamic compression and also of the degree of compression required to prevent further increase in flow. The dashed ordinate in Fig. 12*B* intersects the flow curve at $\dot{V}_{max}$. At this flow EPP would be at the same location as during dynamic compression at maximum flow. Comparison of the resistance upstream with that downstream from EPP in the uncompressed state in Fig. 12*B* gives a rough idea of how far EPP progress. At $\dot{V}_{max}$ total intrathoracic airway resistance (Raw-Ruaw) in the uncompressed state is about

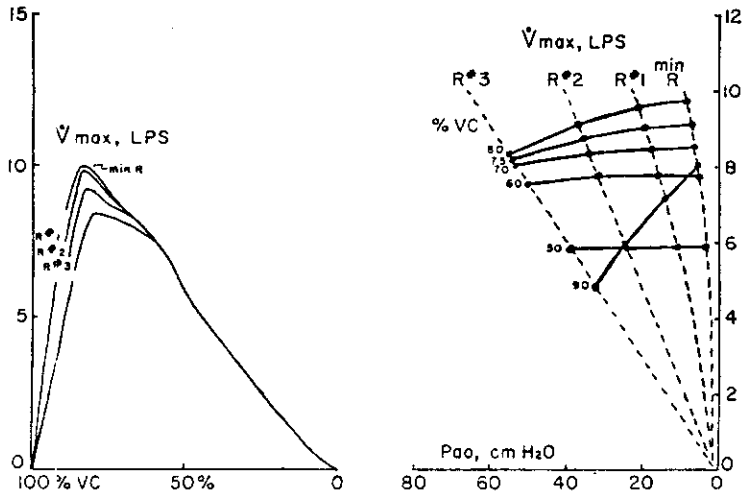

FIG. 13. *A:* average MEFV curves in normal subjects expiring through different resistances. *B:* maximum flow plotted against mouth pressure, Pao, for different resistances and at different lung volumes expressed as % VC.

... intrathoracic resistance downstream from EPP (Rds-Ruaw) is about 0.7 so that EPP are approximately one-third of the way along the total intrathoracic resistance in the uncompressed state at a maximum flow at this lung volume. (At 35% VC EPP were about half way along the total intrathoracic resistance.)

Comparison of the resistance of the compressed segment (Rds-Ruaw) with that of the same segment in the uncompressed state shows that its resistance increases about six times by the time maximum flow is reached. (Compare Rds-Ruaw at $\dot{V}_{max}$ in Fig. 12*A* and *B*). This would require a reduction in cross section of slightly more than 50% in a cylinder in which flow is turbulent.

APPENDIX II

Experiments testing range over which maximum flow is independent of effort. We examined the extent of the effort-independent range with a second method suggested by the work of Hyatt et al. (15). They pointed out that in some circumstances maximum flow would be uninfluenced by additional resistances at the mouth: the effect of additional resistance would be to reduce transpulmonary pressure but as long as this pressure remained equal to or above that necessary to achieve maximum flow, flow would not be changed. Figure 13 represents average data for five subjects who, after maximum inspiration, expired maximally through known resistances. The flow-volume curves are shown on the left. Resistance as great as 5 cm H_2O/LPS had no discernible influence on maximal flow at volumes below 50% of vital capacity.

These same data, together with mouth pressures, can be used to greater advantage to define the maximal volume at which added resistances fail to influence flow. On the right in Fig. 13, flows are plotted against mouth pressure with mouth pressure increasing to the left of the ordinate. We will now show that these curves are essentially segments of IVPF curves.

Since all efforts were maximal, the forces developed by the respiratory muscles at a given volume must have differed only to the extent that the velocity of shortening of the muscles differed at the same volume. We are most interested in the flatter portions of the pressure-flow curves. In these regions the rates of flows differ between resistors by comparatively small amounts. It follows that the velocity of shortening of the muscles must, in this case, be nearly independent of the external resistance. Accordingly, the total driving pressure supplied by the respiratory muscles must, in the flatter portions of the curves, be nearly constant. This total driving pressure is dissipated in the flow resistance of the chest wall, the lungs and airways, and the external resistance. Since flow-resistive losses within the chest wall must be extremely small as compared to those in the airways and external resistances, the pressure developed by the muscles must be very nearly divided between the airways and external resistance. At a given lung volume, then, any increases, as resistance is added, in pressure measured at the mouth must be matched by corresponding decreases in transpulmonary pressure. Accordingly, pressure-flow curves plotted with mouth pressure increasing to the left are comparable to isovolume pressure-flow curves based on transpulmonary pressure.

To recapitulate these ideas; at a fixed lung volume the total driving pressure during maximal expiratory effort should be nearly independent of the amount of external resistance in the range of greatest interest, namely, where maximal flow changes little with external resistance. This driving pressure is, to a close approximation, the sum of transpulmonary pressure and mouth pressure. It follows that, driving pressure being nearly constant, any changes in mouth pressure must be very nearly equal and opposite to changes in transpulmonary pressure and that the curves in Fig. 13*B* are essentially IVPF curves. These are seen to be nearly flat up to volumes of 70% VC. We conclude that the effort-independent range of maximum flow extends to at least 70% of VC, or over most of the declining phase of flow.

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VENTILATORY LIMITATIONS ON EXERTION AT DEPTH

J. N. Miller, O. D. Wangensteen, and E. H. Lanphier

At normal atmospheric pressure the amount of work a man can do seems to be limited by his cardiovascular system (3). At depth, however, alveolar ventilation may be the limiting factor. Increased air density may prohibitively increase flow resistance through a breathing apparatus, or it may limit flow through a man's own airways.

Even if a diver uses superior breathing apparatus, his maximum voluntary ventilation (MVV) decreases markedly with increasing depth, as shown in Fig. 1. This figure is taken from Lanphier (4), who correlated data from the work of Miles (7), Wood (12), Maio and Farhi (5), and Seusing and Drube (10). The greatest difference in the values obtained by Maio and Farhi and by Wood appeared at 1 atm abs, whereas agreement was almost perfect (both about 135 L/min) at 2 atm abs. The average MVV when air is breathed is nearly 200 L/min at the surface, and falls to about half that figure at 4 atm abs.

We contend that the principal factor limiting MVV is the conductance of the airways themselves, rather than a man's ability to expend energy in moving dense gas, as had previously been supposed. The concept of dynamic compression of airways put forward by Fry and Hyatt (1), Mead *et al.* (6), and Pride and his associates (9) explains why airways rather than expiratory effort limit flow.

Figure 2 shows expiratory flow at 50% vital capacity (VC) plotted for pressures of 1, 4, and 7.8 atm abs when breathing air. Each curve is composed of many points obtained from measurements of lung volume, flow, and transpulmonary pressure during expiratory maneuvers ranging from gentle air leaks to maximal forced expirations. Pressure–flow curves were then constructed for isovolumes between 80 and 20% VC. Only the curves for 50% VC isovolume are shown. The crucial factor in expiration is that expiratory flow increases only to a certain point while expiratory effort continues to increase. Large intrathoracic airways then begin to collapse. Beyond that point additional expiratory effort produces no further increase in flow, only an increase in the degree of airway collapse. Maximum flow has become *effort-independent.*

Studies made under conditions of high pressure by Wood *et al.* (11) indicate that effort-independent maximum expiratory flow ($\dot{V}_{max}$) becomes progressively lower as gas density increases. Our own findings confirm theirs in most respects (8).

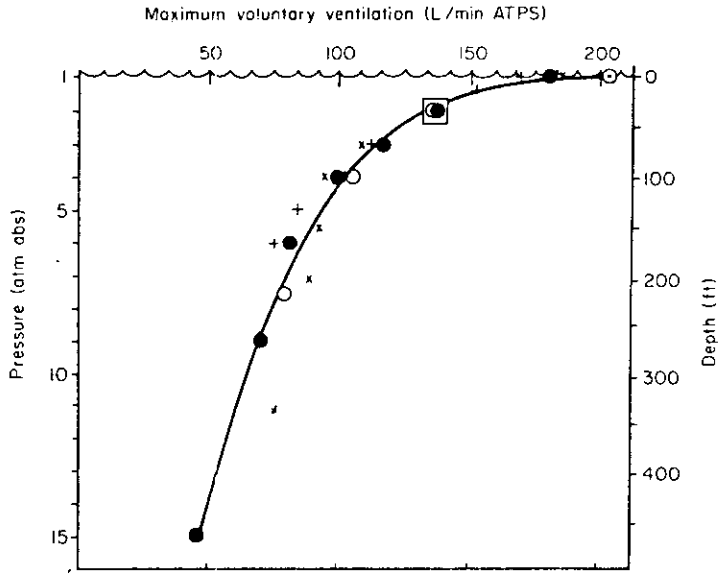

FIG. 1. Maximum voluntary ventilation with air at various depths, from the work of Lanphier (4); values derived from four different studies. (○) Maio and Farhi (5); (●) Wood (12); (×) Miles (7); (+) Seusing and Drube (10). (By permission of publishers.)

It seems certain that limitation of expiratory flow is the main reason for the reduction in MVV shown in Fig. 1. The work of breathing is indeed increased at depth. However, expiratory flow becomes effort-independent before an intolerable effort is required. It is essential at this point to differentiate between the mechanics of the human respiratory system and those of an external breathing apparatus. Airway collapse does not occur without relatively high expiratory flow. The addition of high external resistance in a conventional breathing apparatus

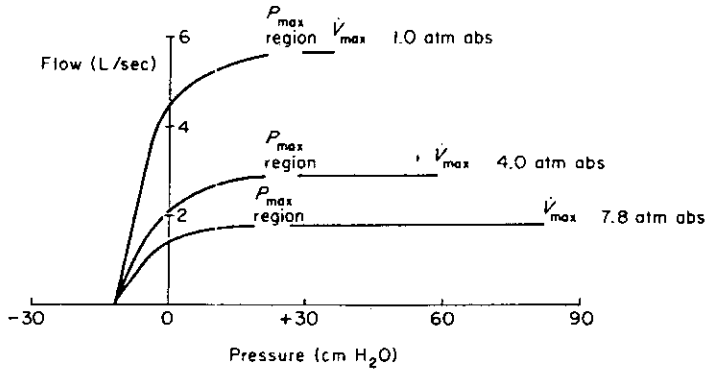

FIG. 2. Pressure–flow curves for 50% vital capacity isovolume at 1, 4, and 7.8 atm abs. Zero flow corresponds to static lung recoil pressure. $\dot{V}_{max}$ is maximum effort-independent flow, and P_{max} is pressure at which flow first becomes effort-independent.

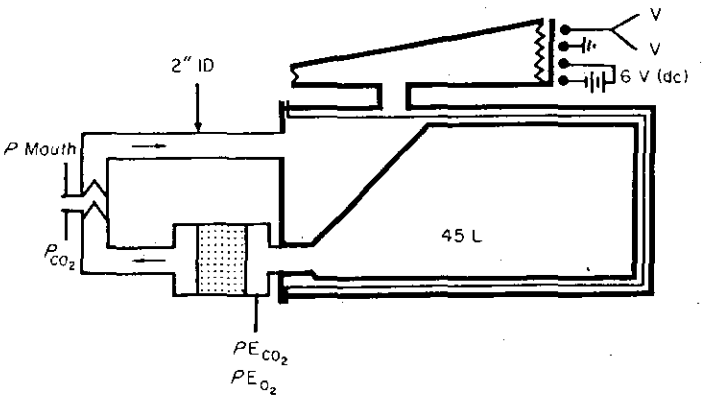

FIG. 3. Low-resistance rebreathing apparatus coupled to a Wedge spirometer. Low-resistance conical breathing valves were developed by Scott Aviation Division, Automatic Sprinkler Corporation of America, Erie Street, Lancaster, New York.

may restrict flow so much that effort limitation actually does occur before flow limitation in the airway occurs.

We have built a low-resistance rebreathing apparatus, which is based on the bag-in-box principle and is coupled to a Wedge spirometer (see Fig. 3). At the surface its resistance is

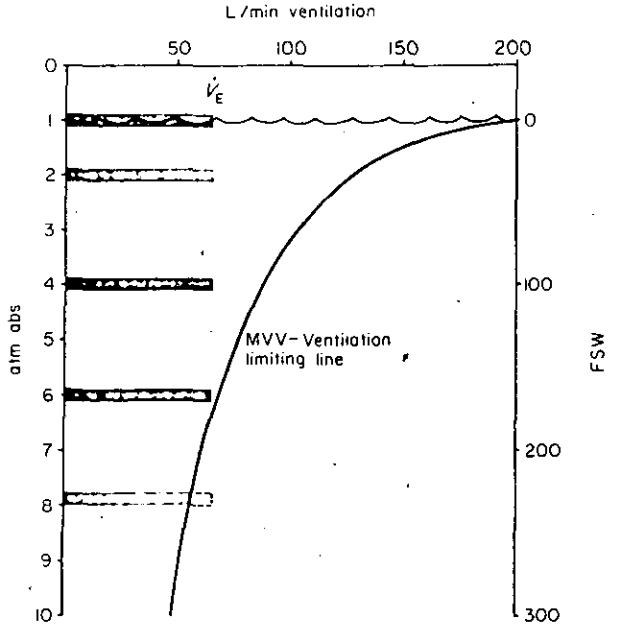

FIG. 4. Ventilation in air atmosphere at various depths. Exercise ventilations are shown as shaded bars. The dashed portion of bar at 7.8 atm abs shows what ventilation was required to prevent CO_2 retention; shaded area shows ventilation actually measured.

about 1/25th that of conventional scuba apparatus, and as depth increases this relationship becomes still more favorable. Dead space in the breathing valve is less than 100 cm^3. An automatic mechanism switches the bag-box connections to allow continuous rebreathing for long periods of time. Carbon dioxide is absorbed in soda lime, and O_2 is added volumetrically as required, based upon continuous gas analysis. We repeatedly measure ventilatory and respiratory variables, including mechanical factors and breath-by-breath CO_2 changes.

We are currently studying the effect of exercise on subjects compressed to the equivalent of 225 FSW (7.8 atm abs) while they breathe air in a pressure chamber. Density of air at 7.8 atm abs is the same as that of an appropriate O_2–He breathing mixture at about 2000 ft. The results reported in this paper pertain to the most complete of a series of experiments performed on four subjects. The data for the subject reported here correlate well with those for the other three subjects.

This subject exercised at a work setting of 200 W, using a bicycle ergometer at surface pressure and at 2, 4, 6, and 7.8 atm abs. This work load is heavy, but submaximal. Oxygen consumption ($\dot{V}_{O_2}$) is 2.8 to 3.0 L/min—heavier than that usually required in diving operations (4).

Minute ventilations ($\dot{V}_E$) during this heavy work load are shown in Fig. 4. The subject's MVV curve is shown, and the bars represent his minute ventilations. There was no marked change in $\dot{V}_E$ until the work was attempted at 7.8 atm abs, where MVV was less than the exercise ventilation required at shallower depths. His $\dot{V}_E$ diminished from 60 L/min at 6 atm abs to 54 L/min at 7.8 atm abs—a fall of 10%.

Figure 5 shows typical curves representing breath-by-breath CO_2 measurements made with an infrared CO_2 analyzer and recorded during the same exercise. There was a slight increase in end-tidal P_{CO_2} (from 36 to 41 mmHg between 1 and 6 atm abs), and a dramatic rise to 50 mmHg at 7.8 atm abs. The rise in P_{CO_2} coupled with the decreased ventilation at 7.8 atm abs indicates that the subject could not ventilate beyond his maximum voluntary level. He then began to retain CO_2 and after 4 min felt so tired and uncomfortable that he stopped work. At shallower depths he easily maintained 6–8 min of exercise, and at no time did he feel the need to stop.

We conclude that heavy work could be done in an air atmosphere at depths greater than 225 FSW (7.8 atm abs) if the diver could tolerate a high degree of CO_2 retention, as some divers can. However, the risk of CO_2 intoxication, particularly when there is a possibility of inert gas narcosis or a high P_{O_2}, could make very heavy work at great pressure extremely hazardous.

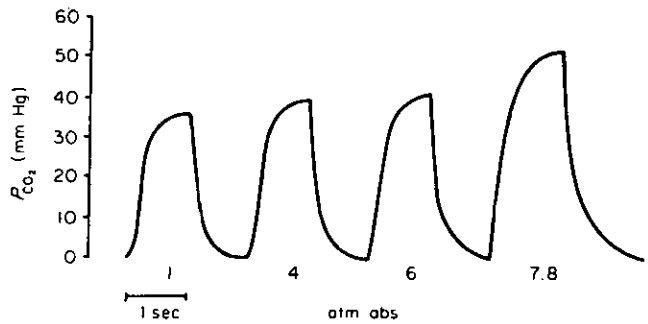

FIG. 5. End-tidal P_{CO_2} records during 200-W exercise at various depths.

Although ventilation during heavy work did not change much with depth down to the MVV, the expiratory effort progressively increased until expiratory-flow limitation developed. At the point of MVV, the subject did not significantly increase his expiratory work. He seemed to limit himself to the minimum effort required to generate maximum flow. Our data so far

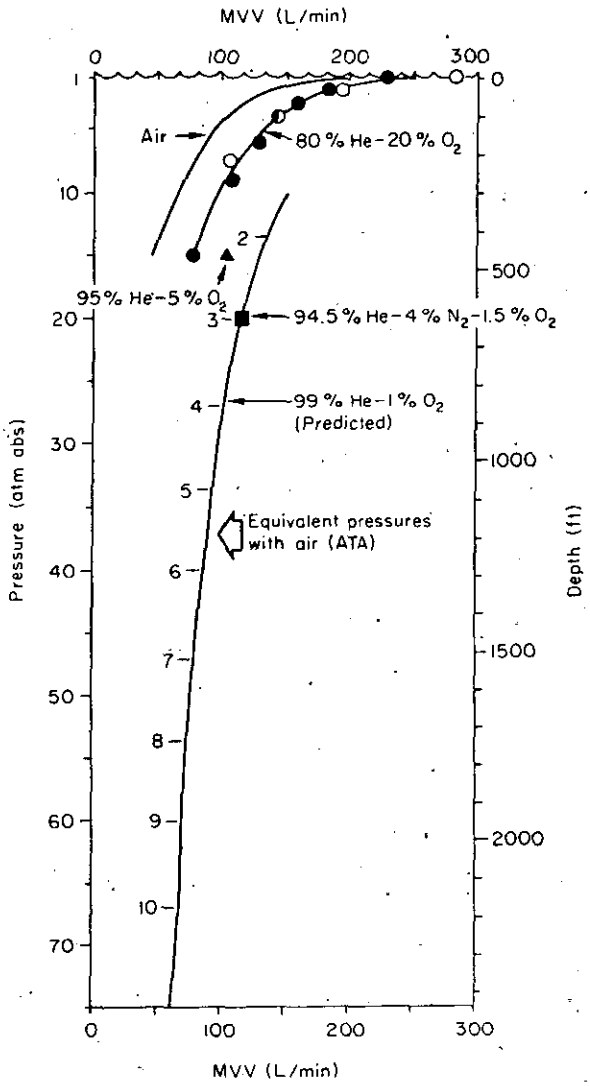

FIG. 6. Actual and predicted values of MVV with $He-O_2$ breathing mixtures, from the work of Lanphier (4) The curve labeled *"99% He–1% O_2 (predicted)" is based on the air* curve in Fig. 1. Air is 6.67 times as dense as the $He-O_2$ mixture. The assumption was therefore made that the MVV values obtained in an air atmosphere at various depths will be obtained at 6.67 times those depths if the breathing mixture is 99% He–1% O_2. (○) Maio and Farhi (5); (●) Wood (12); (▲) Wood (12); (■) Hamilton *et al.* (2). (By permission of publishers.)

suggest that subjects do not waste energy in attempting to maintain ventilation in the face of effort-independent flow.

This same subject also exercised at a lighter load, namely, 100 W. This load required an O_2 consumption of about 1.3 L/min, and is equivalent to such moderate exertion as swimming underwater at a rate of 20–30 yd/min or 0.8 knot (4). Minute ventilation was about the same at depth as it was at the surface. Expiratory flow never became effort-independent. End-tidal P_{CO_2} did not change. Although the subject's ventilation during heavy work in an air atmosphere became limited between 6 and 7 atm abs, it should be possible for a diver to maintain a moderate work load while breathing air at a pressure of 15 atm abs or more.

Predictions can be made regarding the maximum ventilation of subjects who breathe gas mixtures of various densities relative to air. Figure 6, also taken from Lanphier (4), shows actual and predicted values for MVV with $He–O_2$ mixtures.

From our data we conclude that our subject should be able to maintain heavy work to about 45 atm abs (approximately 1500 ft) while breathing a 99% He–1% O_2 mixture. Furthermore, he should be able to perform moderate work at much greater depths than those on the figure—i.e., at about 3500 ft or 100 atm abs. With optimal breathing apparatus, man perhaps may dive to such depths or even deeper.

ACKNOWLEDGMENTS

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c) Zusammenhang der statischen Kräfte von Brustinhalt und Brusthöhlenwandung.

Aus der Gleichung des statischen Kräftezusammenhanges an der Lungenoberfläche (S. 95)

$$p - b = p_{pleur} = p_{musk} + p_{el\,thor} = p_{alv} - p_{el\,pulm}$$

erhält man für Muskelerschlaffung ($p_{musk} = 0$) die Beziehung der passiven statischen Kräfte:

$$p_{el\,thor} = p_{alv} - p_{el\,pulm}, \qquad \text{oder} \qquad p_{alv} = p_{el\,thor} + p_{el\,pulm} = \sum p_{el}.$$

Der Lungenluftdruck bei einer passiven Ruhelage ist gleich dem Summenwert aller passiven Kräfte der Atemorgane.

1. Summenwert der passiven Atemkräfte bei wechselnder Dehnungslage.

Die $\sum p_{el}$-Werte, welche bei Muskelerschlaffung für verschiedene, je $^1/_2$ Liter auseinanderliegende Dehnungslagen an einer erwachsenen männlichen Versuchsperson (28 Jahre) bestimmt wurden, sind für sitzende und liegende Körperhaltung in Abb. 27 dargestellt[1]).

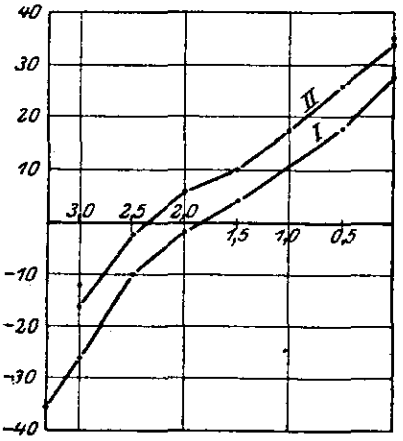

Abb. 27. Abszissenwerte nach links = Exspiration in Litern von maximaler Inspiration aus. Ordinatenwerte = Druck in Zentimetern H_2O bei abgeschlossener Glottis und Muskelerschlaffung. — *I* Kurve der passiven Spannungsresultante im Sitzen. — *II* Kurve der passiven Spannungsresultante im Liegen.

Die $\sum p_{el}$-Werte sind eine *Funktion der Dehnungslage.* Die $\sum p_{el}$-Linie schneidet die Nullabszisse an der Stelle der passiven Ruhelage des Atemsystems bei offener Glottis: passive Normallage, entsprechend der gewöhnlichen Ausatemlage. Oberhalb der Ausatemlage zeigt der $\sum p_{el}$-Druck zunehmend positive, unterhalb der Normallage zunehmend negative Werte. Die Kurve verläuft im mittleren Dehnungsbereich annähernd als schief ansteigende Gerade, gegen die Endlagen hin findet sich ein zunehmend steilerer Verlauf.

Beim Übergang in *liegende Körperhaltung* verschiebt sich die $\sum p_{el}$-Linie annähernd parallel, ohne ihren Charakter zu verändern, zu positiveren Werten (Verminderung des Gewichtszuges der Abdominalorgane). Der Schnittpunkt mit der Nullabszisse, die Ausatemlage, rückt zu einer ca. 0,6 Liter niedrigeren Dehnungslage.

In *Kopfhängelage* liegt die Kurve noch weiter nach oben. Das Anlegen einer inspiratorisch sich spannenden *elastischen Binde* am Thorax bedingt gleichfalls eine Aufwärtsverschiebung der $\sum p_{el}$-Linie, ohne ihren Verlauf wesentlich zu verändern, außer einer unwesentlichen Zunahme der Steilheit.

Im *mittleren Dehnungsbereich*, bis ca. $1^1/_2$ Liter oberhalb und $^1/_2$ Liter unterhalb der gewöhnlichen Ausatemlage, ist die *Summe der passiven Atemkräfte* eine *lineare Funktion der Dehnungslage.*

Wenn in diesem Bereich vom Zustand $\sum p_{el\,o}$ eine Volumänderung von $\pm Q$ Liter erfolgt, ist der am Schluß erreichte Spannungswert

$$\sum p_{el} = \sum p_{el\,o} \pm k_{el} \cdot Q.$$

Die *Spannungsänderung pro Liter Dehnungsänderung* k_{el} beträgt im Sitzen und Liegen für die Versuchsperson 14 cm H_2O.

[1]) Rohrer: Der Zusammenhang der Atemkräfte und ihre Abhängigkeit vom Dehnungszustand der Atemorgane. Pflügers Arch. f. d. ges. Physiol. Bd. 165, S. 425. 1916.

Aus einer früheren Untersuchung BERNOULLIS[1]), welcher die passive Verschiebung der Dehnungslage bei ausgeschalteter Muskelspannung durch wechselnden Außendruck in einer pneumatischen Kammer bestimmte, ergeben sich in zwei Fällen k_{el}-Werte von 12,9 cm H_2O bzw. 14,3 cm H_2O. Zwei weitere Werte von SENNER[2]) und von GERTZ[3]) betragen je 12 cm H_2O.

Nach diesen fünf Bestimmungen scheint für erwachsene männliche Individuen der k_{el}-Wert in geringem Umfang zu schwanken, etwa zwischen 12—15 cm H_2O.

Aus den Angaben BERNOULLIS sind noch folgende Werte zu ermitteln:

13 J. ♂ k_{el} = 19,7 cm H_2O
23 J. ♀ k_{el} = 17, cm H_2O
45 J. k_{el} = 15,3 cm H_2O
48 J. k_{el} = 19,7 cm H_2O.

ROHRER[4]) hat versucht, aus zwei Messungen des maximalen Ausatemdruckes (in maximaler Einatemstellung und einer Dehnungslage ca. $^1/_2$ Liter oberhalb der maximalen Ausatemlage) und der Größe der vitalen Kapazität einen Relativwert für k_{el} abzuleiten, da die direkte Messung des k_{el}-Wertes bei Muskelerschlaffung längere Übung erfordert.

Für 9 männliche Individuen zwischen 11 und 41 J. schwankte der Wert zwischen 11,9—14,7, für 4 Individuen von 47—50 J. zwischen 9,7—11,9. Bei 18 Fällen von Lungenemphysem war der Mittelwert 7,1. Die für die Ausatmung verfügbaren passiven Atemkräfte scheinen im Alter abzunehmen.

2. Die passiven statischen Kräfte der Brusthöhlenumgebung.

Aus der Messung von $\sum p_{el}$ und von $p_{el\,pulm}$ für verschiedene Dehnungslagen, ergibt sich aus der Differenz beider Werte die Größe der passiven Spannung außerhalb des Brustraumes:

$$p_{el\,thor} = \sum p_{el} - p_{el\,pulm} \cdot .$$

In Abb. 28 sind für denselben Fall wie Abb. 27 die Werte graphisch dargestellt.

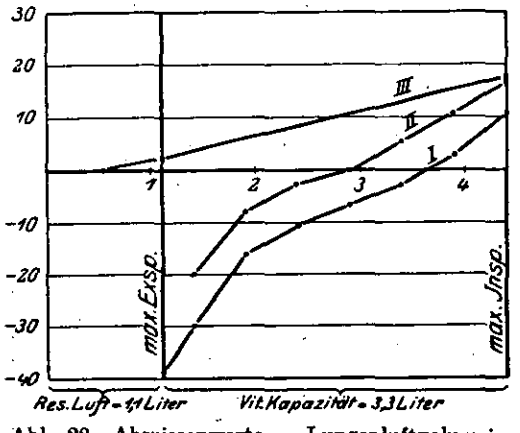

Abb. 28. Abszissenwerte = Lungenluftvolum in Litern. Ordinatenwerte = Druck in Zentimetern H_2O. — *I* Kurve der elastischen Spannung in der Brusthöhlenumgebung im Sitzen. *II* Kurve im Liegen. *III* Linie der elastischen Retraktionskraft des Brustinhaltes.

Die $p_{el\,thor}$-Kurven verlaufen tiefer und weniger steil als die $\sum p_{el}$-Kurven. Der Schnittpunkt mit der Nullabszisse, die Gleichgewichtslage der Brusthöhlenumgebung, liegt gegen die Inspirationslage hin. In aufrechter Körperhaltung wirken die passiven Kräfte der Brusthöhlenwandung, bis ca. $^2/_3$ Liter unterhalb der maximalen Einatemlage, in inspiratorischer Richtung; erst in dem kleinen, letzten Dehnungsbereich in exspiratorischem Sinn. Pro Liter Dehnungsänderung ist die Änderung von $p_{el\,thor}$ im mittleren Dehnungsbereich ca. 9,5 cm H_2O. Von den 14 cm H_2O der $\sum p_{el}$ Änderung pro Liter Dehnung fällt etwa $^2/_3$ auf die Brusthöhlenumgebung, etwa $^1/_3$ (4,5 cm H_2O) auf den Brustinhalt.

Der Verlaufscharakter der $\sum p_{el}$-Kurve und ihre Lage ist durch die $p_{el\,thor}$-Komponente bestimmt.

Die zunehmende Steilheit gegen die Endlagen entspricht dem Auftreten neuer äußerer Spannungsmomente, indem die Bandapparate des Thoraxskelettes und auf der Bauchhöhlenseite inspiratorisch die Bauchdecken, exspiratorisch das Zwerchfell sich ihrer Dehnungsgrenze nähern.

[1]) BERNOULLI: Arch. f. exp. Pathol. u. Pharmakol. Bd. 66, S. 321. 1911.
[2]) ROHRER: Pflügers Arch. f. d. ges. Physiol. Bd. 194, S. 150. 1922.
[3]) GERTZ: Acta med. scandinav. Bd. 56, S. 76. 1922.
[4]) ROHRER: Pflügers Arch. f. d. ges. Physiol. Bd. 165, S. 435. 1916; ferner: Über Lungenemphysem. Münch. med. Wochenschr. 1916, Nr. 34. S. 1219.

Der Einfluß der Körperlage auf die $\sum p_{el}$-Kurve geschieht ebenfalls durch eine Veränderung der $p_{el\,thor}$-Komponente. Im Liegen verschiebt sich die Gleichgewichtslage der Brusthöhlenumgebung in exspiratorischer Richtung (Abnahme des Gewichtszuges des Bauchinhaltes). In gleicher Richtung verschiebt sich die $p_{el\,thor}$-Kurve bei Anbringen einer elastischen Binde am Thorax. Daß in beiden Fällen, trotz Änderung der passiven Kräfte an einer Stelle der Brusthöhlenwandung, die Steilheit der $p_{el\,thor}$-Kurve kaum beeinflußt wird, scheint darauf hinzuweisen, daß die Dehnung des Brustraumes in ihrer Richtung sich der statischen Kräfteverteilung anpaßt, und zwar so, daß die *Bewegung in der Richtung geringster Spannungszunahme* bevorzugt ist. Wahrscheinlich ist die *individuelle Verschiedenheit des Atemtypus* eine solche *Anpassung an die gegebenen statischen Verhältnisse der Brusthöhlenumgebung*, z. B. Vorwiegen kostaler Atmung bei Spannungssteigerung im Bauchraum. Bei Seitenlage auf festem Untergrund ist die abdominelle Atembewegung des Säugetieres auf die nach oben freiliegenden Bauchdeckenabschnitte beschränkt.

Über die *topographische Verteilung* der passiven Atemkräfte in der Brusthöhlenumgebung (elastische Kräfte, Gewichtskräfte) sind wir nur in allgemeinen Umrissen orientiert, aus Untersuchungen an Leichenmaterial, deren Wert bei der Veränderung der physikalischen Eigenschaften der Gewebe nach dem Tod, zum Teil ein bedingter ist (z. B. Arbeit Landerer, Arch. f. Physiologie, 1881, S. 278).

3. Aktive Atemkräfte und Summenwert der passiven und aktiven Atemkräfte.

Bei maximaler inspiratorischer oder exspiratorischer Muskelanspannung in irgendeiner Dehnungslage ist der Wert der Lungenluftspannung $p_{alv\,max}$: nach Gleichung S. 101:

$$p_{alv\,max} = p_{musk} + \sum p_{el}$$

und

$$p_{musk} = p_{alv\,max} - \sum p_{el}.$$

In Abb. 29[1]) sind die bei wechselnder Dehnungslage erhaltenen Werte für dieselbe Versuchsperson wie Abb. 27 und 28 dargestellt.

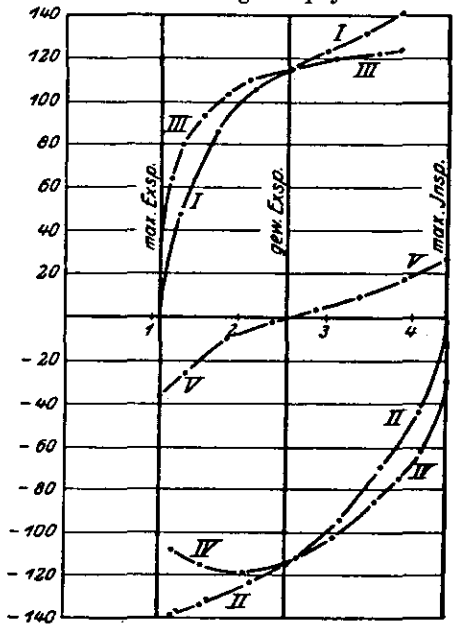

Abb. 29. Abszissenwerte = Lungenluftvolumen in Litern. Ordinatenwerte = Druck in Zentimetern H_2O. — *I* Kurve des maximalen Exspirationsdruckes. *II* Kurve des maximalen Inspirationsdruckes. *III* Kurve der maximalen exspiratorischen Muskelkraft. *IV* Kurve der maximalen inspiratorischen Muskelkraft. *V* Kurve der elastischen Spannungsresultante.

A. Maximaler Atemdruck.

Der maximale Ausatemdruck und maximale Einatemdruck ist von der *Dehnungslage* abhängig.

Der Höchstwert des maximalen Ausatemdruckes wird von maximaler Einatemstellung aus erreicht. Die Kurve I sinkt von hier zunächst langsamer, dann steiler bis zum Nullwert in maximaler Ausatemstellung.

Die Kurve II der maximalen Einatemdrucke zeigt einen gleichmäßigen, gebogenen Verlauf in umgekehrter Richtung.

[1]) Rohrer: Pflügers Arch. f. d. ges. Physiol. Bd. 165, S. 433. 1916.

Von SENNER[1]) wurde ein ähnlicher Verlauf der beiden Kurven festgestellt.

Die individuelle Variabilität der Grenzwerte des maximalen Ausatemdruckes in Inspirationslage und maximalen Einatemdruckes in Exspirationslage liegt nach den Messungen einer Reihe von Untersuchern im Bereich[2]):

positiver maximaler Ausatemdruck ♂ 60—150, ♀ 30—80 mm Hg,
negativer maximaler Einatemdruck ♂ 50—120, ♀ 25—60 mm Hg.

Im allgemeinen ist der positive Wert des maximalen Ausatemdruckes beim selben Individuum höher als der negative Wert des maximalen Einatemdruckes. Der maximale Atemdruck ist außer von der Dehnungslage auch vom Zustand der Muskulatur (Übung, Ermüdung) abhängig.

B. Die maximalen Muskelkräfte.

Ihre Abhängigkeit von der Dehnungslage ist durch Kurve III und IV dargestellt. Die Kurve III der exspiratorischen muskulären Maximalspannung hat ihren Höchstwert in Inspirationslage, wo diese Muskeln die größte Ausgangslänge besitzen. In gewöhnlicher Ausatemlage ist $\sum p_{el} = 0$, daher $p_{alv\,max} = p_{musk}$: Kreuzung der Kurven. Die Kurve senkt sich langsam gegen die Ausatemlage hin, wo sie plötzlich abfällt zu einem Wert, welcher gleich und entgegengesetzt dem hier vorhandenen $\sum p_{el}$-Wert ist. Der letzte steile Abfall ist wahrscheinlich dadurch bedingt, daß mit dem Sinken des Thorax und Steigen des Zwerchfells für die Bauchwandmuskeln die Bedingungen der Kraftentfaltung zunehmend ungünstiger werden.

Die Kurve IV des maximalen, inspiratorischen Muskelzuges verläuft abfallend gegen die Einatemstellung hin. Das raschere Sinken gegenüber der Kurve III ist hier vielleicht dadurch bedingt, daß die Fläche, auf welche der Druck ausgeübt wird, die Brusthöhlenoberfläche, inspiratorisch wächst. Der Druckanteil der Oberflächeneinheit vermindert sich entsprechend, während er exspiratorisch durch die Flächenabnahme sich vergrößert.

Das primäre Ansteigen der Kurve zwischen maximaler und gewöhnlicher Ausatemstellung ist wahrscheinlich darauf zu beziehen, daß hier zunächst, durch Erweiterung der unteren Brustkorbapertur, für das Zwerchfell die Arbeitsbedingungen günstiger werden. [Diesen primären Anstieg der inspiratorischen Muskelspannungskurve findet auch SENNER[3]).]

C. Statischer Pleuradruck bei Tätigkeit aktiver Atemkräfte.

Der statische Pleuradruck $p_{pleur} = p_{alv} - p_{el\,pulm}$ entspricht bei offenen Luftwegen ($p_{alv} = 0$) der elastischen Lungenspannung und hat entsprechend unter diesen Verhältnissen einen mit der Dehnungslage proportional sich ändernden Wert.

Wenn muskuläre, inspiratorische oder exspiratorische Kräfte hinzutreten, kann bei jeder Dehnungslage p_{alv} in weitem Umfang zwischen den Grenzwerten des maximalen Einatem- und Ausatemdruckes sich ändern. Da die Größe der Lungenspannung gegen diese pneumatischen Drucke zurücktritt, verlaufen die Kurven der extremen statischen Pleuradruckwerte bei maximaler inspiratorischer und exspiratorischer Muskelspannung nahe den Kurven I und II in Abb. 29.

d) Die an der Gesamtoberfläche der Brusthöhle wirkenden Kräfte.

Die statischen Atemkräfte werden gemessen als Druckdifferenzen an der Oberflächeneinheit der Brusthöhle. Ihr Produkt mit der Oberflächengröße ist der ausgeübte Gesamtdruck.

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[1]) SENNER: Über Atmung in bewegter Luft. Pflügers Arch. f. d. ges. Physiol. Bd. 190, S. 100. 1921. Ferner ROHRER: ebenda Bd. 194, S. 150. 1922.

[2]) WALDENBURG: Die pneumatische Behandlung S. 39. Dort ältere Literatur. Berlin: August Hirschwald 1880. — Die noch von BORUTTAU (Nagels Handb.) zitierten Werte von VALENTIN sind sicher zu hoch (exspiratorischer Druck bis 256 mm Hg! wahrscheinlich durch Schleuderung).

[3]) SENNER: Pflügers Arch. f. d. ges. Physiol. Bd. 190, S. 100. 1921.

Die Brusthöhlenoberfläche[1]) für dieselbe Versuchsperson wie in Abb. 27, 28 u. 29 bestimmte sich in maximaler Ausatmung, gewöhnlicher Ausatmung und maximaler Einatmung zu 14,9; 18,5 bzw. 22,5 qdm.

Die Kurven des passiven und aktiven muskulären Gesamtdruckes und ihrer Summe verlaufen ähnlich wie die Kurven in Abb. 29[2]).

Die *passiven Kräfte* üben in maximaler Einatemstellung einen Druck von 63 kg, in maximaler Ausatemstellung einen Zug von 53,5 kg an der Brusthöhlenoberfläche aus.

Der höchste *inspiratorische muskuläre Gesamtdruck* ist in gewöhnlicher Ausatemlage 210 kg. Der *maximale inspiratorische Druck* (aktive + passive Kräfte) liegt bei einer etwas niedrigeren Dehnungslage und beträgt 220 kg.

Der größte *muskuläre exspiratorische Druck* in maximaler Einatemstellung ist 266 kg, der *Gesamtdruck* (aktiv + passiv) 305 kg.

Von DONDERS[3]) wurde die maximale Kraftleistung der Atemmuskeln auf über 200 kg geschätzt; nach FICK[3]) sind allein die Musculi intercostales ext. einer Kraftentwicklung von ca. 94 kg fähig.

e) Einfluß der statischen Kräfte auf die Formverhältnisse der Brusthöhlenwandung.

1. Wirkung der Lunge auf die Brusthöhlenwand.

A. Lungenelastizität.

Lunge und Brusthöhlenwandung befinden sich in Gegenspannung. Die Lunge ist dauernd über ihre elastische Gleichgewichtslage gedehnt. Umgekehrt ist das Brusthöhlenvolumen, mit Ausnahme tiefster Inspirationslage, unter die durch die passiven Kräfte ihrer Wandungen gegebene Ruhelage verkleinert.

Der Zug der Lunge an der Brusthöhlenwandung zeigt sich durch die *Ansaugung aller nachgiebigen Wandungsabschnitte:* Sie werden in die Brusthöhle vorgewölbt, bis ihre elastische Spannung dem Lungenzug Gleichgewicht hält. Diese Gewölbeform findet sich beim *Zwerchfell* wie auch bei den *intercostalen Weichteilen*, soweit sie dem Lungenzug ausgesetzt sind. Die Hin- und Herverschiebung des unteren Lungenrandes an der Brustwand, im Bereich des Sinus phrenicocostalis, kann oft als Wanderung dieser Einziehung der intercostalen Weichteile beobachtet werden.

Das *Littensche Zwerchfellphänomen*, die Wanderung einer Einziehung der Zwerchfellansatzstelle an der Wand des Brustkorbes unterhalb des Lungenrandes, welche gleichsam eine verschiebliche funktionelle Insertion des Muskels darstellt, ist von dieser Erscheinung nach SAHLI und STAEHELIN[4]) zu trennen. Die LITTENsche Einziehung bewegt sich mit der Stelle der Zwerchfellanheftung. Sie schiebt sich inspiratorisch abwärts, wobei mit dem Nachrücken der Lunge die Intercostalräume wieder sich ausebnen.

Die elastische Spannung von dehnbaren Brustwandstellen durch den Lungenzug bedingt eine Straffung, Verfestigung. Ob die Brustwand als Ganzes eine Verfestigung erfährt, ist fraglich. Wenn man die Thoraxwand schematisch als homogenes, zylindrisches Gewölbe betrachtet [BECHER[5])], ergibt sich eine tangentiale Pressung, welche proportional dem Lungenzug und dem Gewölberadius ist. Bei einem Brustkorbradius von 10 cm, einem Lungenzug von 10 cm H_2O und einer Wandungsdicke von 2 cm berechnet sich die tangentiale Gewölbepressung auf ca. 50 g pro qcm. In der inhomogen gebauten Thoraxwand werden

[1]) ROHRER: Bestimmung des Inhaltes und der Oberfläche des Brustraumes beim Lebenden. Pflügers Arch. f. d. ges. Physiol. Bd. 165, S. 445. 1916.

[2]) ROHRER: l. c. S. 441. Die Figur ist dort verkehrt gedruckt.

[3]) R. DU BOIS-REYMOND: Mechanik der Atmung. Ergebn. d. Physiol. Bd. I, 2, S. 402. 1902.

[4]) MOHR u. STAEHELIN: Handb. d. inn. Med. Bd. II, S. 209 u. 247. 1914.

[5]) BECHER: Thoraxwandstützende Funktion der Lunge. Mitt. a. d. Grenzgeb. d. Med. u. Chirurg. Bd. 33, S. 257. 1921.

diese Pressungen von den Rippen getragen. Wenn dadurch eine Verfestigung der Brustwand gegeben wäre, müßte dieselbe inspiratorisch, bei zunehmendem Lungenzug beständig starrer, weniger leicht deformierbar werden. Tatsächlich ist jedoch das elastische Verhalten, wenigstens der Brusthöhlenwand als Ganzes, in einem ausgedehnten mittleren Dehnungsbereich ein konstantes (S. 101). Ein gleicher Volumzuwachs bedingt im ganzen Bereich überall eine gleiche Spannungsänderung.

Der Lungenzug wirkt auch auf die Wirbelsäule und fördert die Vorbiegung im thorakalen Abschnitt. Bei dauernd erhöhter Dehnungslage wird durch die Zunahme des Lungenzuges die Brustwirbelsäulenkrümmung verstärkt[1]).

Die Veränderung einer Komponente der Gegenspannungsbeziehung zwischen Lunge und Brustwand unter pathologischen Verhältnissen verschiebt die passive Gleichgewichtslage des Atemsystems: Schrumpfung der Lunge, also Zunahme des Lungenzuges, erniedrigt die Ausatemlage. In gleichem Sinne wirkt Erschlaffung oder Verkleinerung der Brustwand (z. B. Thorakoplastik).

Erschlaffung der Lunge oder Starrerwerden des Brustkorbes verschiebt die Ausatemlage in inspiratorischer Richtung (Emphysem). Die Zwerchfellsenkung und Streckung wird dabei auch durch die Dehnung der unteren Thoraxapertur und durch eine Erschlaffung der Bauchdecken gefördert.

B. Wirkung des pneumatischen Druckes der Lunge.

Der pneumatische Druck kann in jeder Dehnungslage erhebliche Schwankungen aufweisen, exspiratorisch hohe positive, inspiratorisch erhebliche negative Werte besitzen. An den dehnbaren Stellen der Brusthöhlenwand können auffallende Formänderungen bedingt sein, z. B. Einziehung der Intercostalräume und des Epigastriums in der Inspirationsphase bei Stenosenatmung, Vorwölbung der supraclaviculären Weichteile durch den positiven Lungendruck beim Husten.

2. Wirkung der statischen Kräfte der Brusthöhlenwandung.

A. Passive Kräfte.

Die passiven Kräfte ändern sich teils mit der Dehnungslage, teils mit der Körperstellung. Es sind dadurch Rückwirkungen auf die Brusthöhlenwandung bedingt.

Die wechselndsten Lage- und Formverhältnisse besitzt das *Zwerchfell*, indem hier der Einfluß der statischen Kräfte des Brustraumes mit der je nach der Körperlage *veränderlichen Wirkung der passiven Kräfte des Abdomens* zusammentrifft. Der Zug des Brustinhaltes nach oben überwiegt stets den Zug des Bauchinhaltes nach unten, auch in aufrechter Körperhaltung, wo die Gewichtskräfte des Abdomens direkt als Gegenzug wirken.

Der *Bauchinhalt* wird in dieser Stellung teils von den vorgewölbten, elastisch oder tonisch muskulär gespannten Bauchdecken getragen, teils hängt er an mesenterialen Anheftungen. Der Druck im Peritonealraum ist unten am größten. Er nimmt aufwärts ab bis zum Nulldruck in einer horizontalen Schicht oberhalb des Nabels. Erst unterhalb des Zwerchfells besteht negativer Druck. Die im Stehen hier vorhandene Ansaugung zeigt sich in der dauernden Entfaltung des obersten Abschnittes des leeren Magenschlauches (Magenblase). Beim Übergang vom Liegen in aufrechte Körperhaltung führt die Ausbildung dieser negativen Druckzone im oberen Bauchraum zu einer Abnahme des Bauchumfanges an dieser Stelle[2]). Nach eigenen Messungen an Kaninchen besitzt der negative Druck unterhalb des Zwerchfells jedoch stets geringere Werte als der negative Pleuradruck oberhalb des Diaphragmas[3]).

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[1]) HOFBAUER: Atmungspathologie S. 141. 1921.

[2]) PROPPING: Bedeutung des intraabdominellen Druckes. Arch. f. klin. Chirurg. Bd. 92, 2, S. 1072. 1910.

[3]) Arbeit NAKASONE: Über Abdominaldruck. Noch nicht publiziert.

Der negative, subdiaphragmale Druck wird beim Übergang in Rückenlage oder Bauchlage leicht positiv. In Kopfhängelage erhöht sich dieser positive Druckwert beträchtlich. Folgende eigene Messung am Kaninchen an drei Stellen des Bauchraumes belegt diese Tatsache und zeigt zugleich das Bestehen einer hydrostatischen Druckschichtung im Abdomen, welche mit der Körperlage wechselt (Tab. 4).

Tabelle 4.

Druck in cm H_2O (Mittelwert)	Aufrechte Stellung	Rückenlage	Kopfhängelage
epigastrisch	−0,6	+2,4	+6,1
mesogastrisch	+2,6	+2,5	+2,9
hypogastrisch	+4,9	+2,5	+1,5

Der Pleuradruck in aufrechter Stellung war −4,7 cm H_2O, also immer noch beträchtlich den negativen Wert des abdominellen Druckes (−0,6 cm H_2O) überwiegend.

Entsprechend der Steigerung des subdiaphragmalen Druckes in Rückenlage und Kopfhängelage verschiebt sich das Zwerchfell dem Lungenzug folgend kopfwärts.

Beim Menschen beträgt die kraniale Verschiebung des Zwerchfells in Rückenlage nach röntgenologischen Messungen ca. 2 cm gegenüber dem Zwerchfellstand in aufrechter Körperhaltung[1]). Die rechtsseitige Zwerchfellkuppe hebt sich etwas stärker, so daß der Höhenunterschied beider Kuppen im Liegen ausgeprägter wird.

Das verschiedene Verhalten der vorderen und hinteren, rechten und linken Zwerchfellpartien in horizontaler Stellung bei Rückenlage, Bauchlage, rechter und linker Seitenlage erklärt sich ungezwungen aus der hydrostatischen Druckschichtung im Bauchraum, welche jetzt senkrecht die Zwerchfellebene schneidet. Der jeweils unten liegende Zwerchfellabschnitt erleidet einen höheren Gewichtsdruck vom Bauchinhalt und ist entsprechend weiter in den Brustraum vorgeschoben.

B. Aktive Kräfte.

Ihr Einfluß zeigt sich beim Brustkorb in den Formunterschieden aktiv inspiratorischer und aktiv exspiratorischer Dehnungslagen (S. 81).

Das *Zwerchfell* wird im allgemeinen durch die Kontraktion seiner Muskelfasern nur in caudaler Richtung verschoben, die Wölbung bleibt dagegen erhalten. Nur wenn künstlich durch faradische Phrenicusreizung eine maximale Zwerchfellkontraktion ausgelöst wird, zeigt sich eine deutlichere Abflachung der Wölbung, besonders bei einseitiger Reizung, wo der Bauchinhalt nach der anderen, nicht tätigen Seite in gewissem Umfang ausweichen kann.

Das Erhaltenbleiben der Wölbung des tätigen Zwerchfells erklärt sich aus der Angriffsrichtung der überwundenen Gegenkraft. Die Lungenspannung greift radiär am Gewölbe an, die Muskelspannung an dem einzelnen Flächenelement tangential. Eine muskuläre Anspannung führt nicht zu einer Streckung des Gewölbes, sondern zu einem Tieferrücken der verschieblichen Insertion des Muskels am oberen Rand des Sinus phrenicocostalis, unter Einbeziehung neuer, vorher der Brustwand anliegender Abschnitte, weil diese Ablösung von der Brustwand geringere Kraft erfordert. Die tangentiale Spannung, die einem radiären Zug Gleichgewicht hält, wächst mit dem Radius eines Gewölbes bis zu unendlicher Größe bei vollständiger Ausebnung der Wölbung. Die Ablösung von der Brustwand unter Verschiebung des Zwerchfells nach abwärts erfordert dagegen nur eine der Zunahme des Lungenzuges entsprechende Steigerung der Muskelspannung.

Die Wirkung der aktiven Kräfte ist beim Zwerchfell abhängig von der Form und Lage, welche es durch den Einfluß der passiven Kräfte besitzt. Die respiratorische Bewegung ist in horizontaler Körperstellung stets am größten an der unten liegenden Zwerchfellpartie, welche am weitesten in den Brustraum

[1]) Jamin, in Groedel: Röntgendiagnostik in der inneren Medizin S. 105. 1914.

verschoben ist[1]). In Seitenlage betrifft die inspiratorische Senkung fast nur die Zwerchfellkuppe der aufliegenden Seite.

Der Einfluß der aktiven statischen Kräfte auf die Formverhältnisse von Brustkorb und Abdomen wird vor allem deutlich bei einem Ausfall der Funktion einzelner Muskeln oder Muskelgruppen, wo kompensatorisch andere Muskeln in erhöhte Tätigkeit treten, ferner bei beständiger tonischer Innervation von Muskeln (z. B. Erhöhung der Ausatemlage durch tonische Innervation des Zwerchfells).

V. Dynamik der Atembewegung.

a) Dynamische Atemkräfte.

Bei irgendeinem Dehnungszustand der Atemorgane, welcher Durchgangsphase einer Atembewegung ist, wirken außer den vorhandenen statischen Kräften (p_{musk}, $p_{el\,thor}$, p_{alv}, $p_{el\,pulm}$) auch *die Bewegung hemmende Kräfte*, welche der Verschiebung in der Bewegungsrichtung einen Widerstand entgegensetzen.

In die Gleichung des Kräftezusammenhanges an der Kontaktfläche zwischen Brusthöhleninhalt und Brusthöhlenwandung treten dadurch auf beiden Seiten neue Komponenten ein. Die *Widerstandskräfte* liegen teils in der *Körperwandung* $p_{w\,thor}$, teils im *Lungengewebe* $p_{w\,pulm}$, teils in den *Atemwegen* $p_{w\,strom}$. Von diesen drei dynamischen Kräftegruppen ist die erste auf der thorakalen Seite, die zweite auf der pulmonalen Seite in die Gleichung einzusetzen. Die dritte Gruppe, die Strömungswiderstände in den Atemwegen, wirken nur mittelbar auf den Kräftezusammenhang an der Lungenoberfläche zurück, indem die Größe der alveolaren Druckdifferenz p_{alv} mit ihnen in Beziehung steht. Sie sind also bereits durch p_{alv} in der Gleichung vertreten.

Die Gleichung des statischen Kräftezusammenhanges (S. 95)

$$p - b = p_{pleur} = p_{musk} + p_{el\,thor} = p_{alv} - p_{el\,pulm}$$

geht unter dynamischen Verhältnissen in die Form über

$$p - b = p_{pleur} = p_{musk} + p_{el\,thor} + p_{w\,thor} = p_{alv} - p_{el\,pulm} + p_{w\,pulm}.$$

Die Widerstandskräfte sind inspiratorisch mit negativem, exspiratorisch mit positivem Vorzeichen in die Gleichung einzusetzen.

Über diese dynamischen Kräfte, ihre Abhängigkeit vom Bewegungszustand (Geschwindigkeit, Beschleunigung) und ihre Größenordnung sind zunächst einige allgemeine Feststellungen möglich.

1. Der Strömungswiderstand in den Atemwegen.

Bei offenen Luftwegen wirkt die Druckdifferenz zwischen Lungenluft und Außenluft (p_{alv}) als Triebkraft der Atemluftströmung.

Die ausführenden Luftwege der Lungenlufträume sind ein verzweigtes Röhrensystem aus im allgemeinen zylindrischen Rohrelementen. Die Strombahn besitzt in den oberen Luftwegen Krümmungen (Übergang von Nase zu Pharynx) und Querschnittsänderungen (Glottis). Bei den Verzweigungen in den unteren Luftwegen sind ebenfalls Änderungen der Querschnittsgröße des Strombettes und Richtungsänderungen vorhanden.

A. Rohrströmung.

Die Strömungsleistung in der einzelnen Rohrstrecke, das pro Sekunde transportierte Volum, ist abhängig von der Druckdifferenz zwischen den Rohrenden, von den Abmessungen des Rohres (Länge l, Querschnitt F) und den Eigenschaften des strömenden Mediums (Viscosität η). Ferner ist der Strömungscharakter maßgebend. Bis zu einer oberen Grenze der Strömungsgeschwindigkeit, der *kritischen Geschwindigkeit*, herrscht Parallelströmung. Druckdifferenz (p) und Volumgeschwindigkeit (V) besitzen ein direktes proportionales Verhältnis (POISEUILLEsche Strömung).

$$p = k_1 \cdot w_1 \cdot \eta \cdot V$$

$$\left(w_1 = \frac{l}{F^2} = \text{Rohrwiderstand};\ \eta = \text{Viscosität}\right).$$

[1]) JANIM: l. c. S. 108, ferner Abb. 67 und 68.

Oberhalb der kritischen Geschwindigkeit besteht Wirbelströmung (*Turbulenz*). Die Druckdifferenz ist von einer Potenz der Volumgeschwindigkeit abhängig.

Die *kritische Geschwindigkeit wird bei der Atmung in den Luftwegen nie erreicht* (Ausnahme beim Hustenstoß), die Strömung erfolgt nach dem POISEUILLEschen Gesetz[1]).

B. Die Extrawiderstände.

Durch Querschnitts- und Richtungswechsel sind Druckdifferenzen bedingt, welche vom Quadrat der Strömungsgeschwindigkeit, vom spezifischen Gewicht des strömenden Mediums und von räumlichen Bedingungen abhängen (Größe des Querschnittswechsels, Ablenkungswinkel):

$$p = k_2 \cdot w_2 \cdot \gamma \cdot V^2$$

[w_2 = Extrawiderstand; γ = spezifisches Gewicht].

C. Strömung in einem Röhrensystem.

Zwischen Strömungstriebkraft (p) und Volumgeschwindigkeit (V) besteht eine Beziehung von der Form:

$$p = k_1 \cdot w_1 \cdot \eta \cdot V + k_2 \cdot w_2 \cdot \gamma \cdot V^2 .$$

w_1 ist die Summe der Rohrwiderstände des Systems, w_2 die Summe der Extrawiderstände[2]).

Die *Viscosität* der Atemluft beträgt für alle in Frage kommenden Verhältnisse[3]) (Inspiration, Exspiration, Tiefenklima, Höhenklima bis 2000 m, Fieber bis 43°):

$$\eta = 0{,}0001873 \text{ dyn.}$$

Das *spezifische Gewicht* γ der Atemluft ist für Einatemluft und Ausatemluft annähernd gleich. Es wechselt mit dem Luftdruck. (Höhenklima, Ballonfahrten, Caissonarbeiten.) Die Abnahme von γ im *Höhenklima* bedeutet eine Verringerung der Extrawiderstände in den Atemwegen, welche, da es sich um das quadratische Glied der Formel handelt, besonders bei hoher Minutenleistung der Atmung fühlbar wird (z. B. für Höhenlage des Engadins Abnahme der Extrawiderstände auf ca. $^4/_5$).

D. Strömungsgleichung der Luftwege.

Für die *Luftwege des erwachsenen Menschen* bei Nasenatmung hat ROHRER[4]) aus den durch anatomische Messungen gegebenen Längen- und Querschnittsverhältnissen der einzelnen Abschnitte die Beziehung zwischen alveolärer Druckdifferenz zur Außenluft (p_{alv}) und Volumgeschwindigkeit ($V_{\text{Liter/Sek.}}$) berechnet:

$$p_{alv} = 0{,}8\,(V + V^2) \text{ cm } H_2O .$$

Der Druckanteil der *oberen Luftwege* beträgt:

$$p = 0{,}43\,V + 0{,}71\,V^2 ,$$

derjenige der *unteren Luftwege* zwischen Trachea und Lungenluft:

$$p = 0{,}36\,V + 0{,}09\,V^2 .$$

Die Dimensionszunahme der intrapulmonären Bronchen bei der Lungendehnung verläuft wahrscheinlich so, daß der Strömungswiderstand sich nicht wesentlich ändert. (Zurückbleiben der Querschnittsdehnung der Bronchen gegenüber der Längendehnung.)

Bei ruhiger Atmung ($V = {}^1/_2$ bis ${}^1/_2$ Sek./Liter) ist die alveoläre Druckdifferenz: 0,4—0,6 cm H_2O; bei maximaler Atmung ($V = 2{,}1$ bis 3,5 Sek./Liter) ist p_{alv}: 5—13 cm H_2O (Abb. 7).

Oberhalb $V = 5$ Liter/Sek. beginnt turbulente Strömung und wird p proportional V^2. Beim Hustenstoß [nach GEIGEL[5]) zu Beginn $V = 12$ Liter] ist p_{alv} = ca. 140 cm H_2O, entsprechend der Größe des maximalen Ausatemdruckes.

Eine *experimentelle Bestimmung von* p_{alv} stößt auf Schwierigkeiten, da bei Bewegungszuständen nicht nur die statische elastische Spannung der Lunge

[1]) ROHRER: Der Strömungswiderstand in den menschlichen Atemwegen. Pflügers Arch. f. d. ges. Physiol. Bd. 162, S. 236. 1915.

[2]) Summationsgesetze für hintereinandergeschaltete und für parallelgeschaltete Strecken siehe ROHRER: l. c. S. 241—246.

[3]) ROHRER: l. c. S. 228—230.

[4]) ROHRER: l. c. S. 249—281.

[5]) GEIGEL: Virchows Arch. f. pathol. Anat. u. Physiol. Bd. 161, S. 182.

wechselt, sondern auch Reibungswiderstände im Lungengewebe ($p_{w\,pulm}$) mit in Frage kommen.

Nach der Gleichung der pleuralen Druckdifferenz

$(p_{pleur} = p_{alv} - p_{el\,pulm} + p_{w\,pulm})$ ist: $p_{alv} + p_{w\,pulm} = p_{pleur} + p_{el\,pulm}$

gleich der Summe von pleuraler Druckdifferenz und statischer Lungenspannung (unter Berücksichtigung der Vorzeichen ihre Differenz).

ROHRER und WIRZ[1]) haben an der isolierten Kaninchenlunge eine Bestimmung der Strömungsgleichung $p_{alv} = k_1 \cdot w_1 \cdot \eta \cdot V + k_2 \cdot w_2 \cdot \gamma \cdot V^2$ versucht, indem sie die Lungenluft durch Flüssigkeit ersetzten[2]). Der Anteil des Strömungsdruckes wird so gesteigert, daß die Reibungswiderstände im Gewebe dagegen zu vernachlässigen sind. Da p_{alv} und V experimentell gegeben sind, ebenso η und γ der Flüssigkeit, ist $k_1 \cdot w_1$ und $k_2 \cdot w_2$ bestimmbar und kann durch Einsetzen von η und γ der Atemluft die Strömungsgleichung für Luftströmung in den Atemwegen abgeleitet werden.

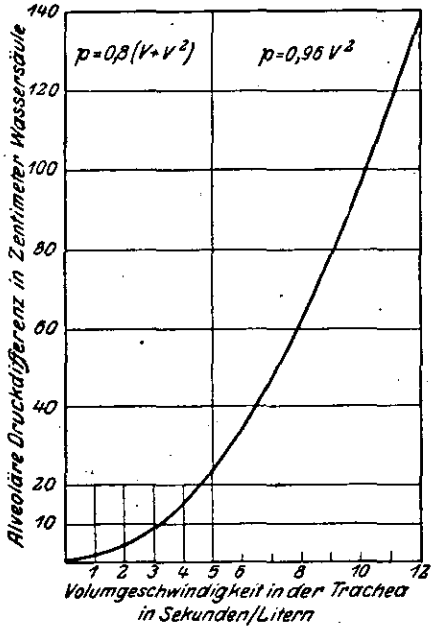

Abb. 30. Alveoläre Druckdifferenz bei verschiedenen Volumgeschwindigkeiten in den Luftwegen.

Für die intrapulmonären Luftwege von 10 g schweren *Kaninchenlungen* (Tiergewicht ca. 2 kg) bestimmte sich die Strömungsdruckdifferenz zu:

$$p_{cm}\ H_2O = 0{,}007\ V + 0{,}0003\ V^2\ (V_{ccm/Sek.}).$$

Die Druckdifferenz zwischen Trachea und Lungenluft beträgt bei den Volumgeschwindigkeiten 20, 40, 60 und 80 ccm pro Sek.

$$p = 0{,}25,\ 0{,}8,\ 1{,}6 \text{ und } 2{,}6 \text{ cm } H_2O.$$

Für ruhige Atmung (V = ca. 20 ccm/Sek.) ist p: $^1/_4$ cm H_2O.

Für die Luftwege des Menschen ist bei ruhiger Atmung die Druckdifferenz zwischen Trachea und Lungenluft nach Berechnung ca. $^1/_5$ cm H_2O (siehe oben Strömungsformel der unteren Luftwege).

Eine Vergleichung der experimentell bestimmten Strömungsformel der Kaninchenlunge und der berechneten Formel der menschlichen Lunge ist auch in folgender Weise möglich: Wenn man das Parenchymgewicht beider Lungen des Menschen zu ca. $^2/_3$ des Lungengewichtes rechnet (ca. 400 g) und annimmt, daß jeder Bezirk von 10 g dieselben Strömungs-

[1]) ROHRER u. WIRZ: Die Bestimmung des Strömungswiderstandes in den Atemwegen auf experimentellem Wege. Noch nicht publiziert. — Ergebnisse mitverwendet in WIRZ: Über Pleuradruck. Pflügers Arch. f. d. ges. Physiol. Bd. 199, S. 43. 1923.

[2]) Das Verfahren besteht in einer Ersetzung der Lungenluft durch Kohlensäure, unter Anwendung eines Überdruckventiles (10 bis 15 cm H_2O) und 15 bis 20maliger Füllung der Lunge. Absorption der Kohlensäure durch $^1/_{40}$ n-Barytlauge, welche mit Rohrzucker dem Gewebe isotonisch gemacht ist (NaCl ist ungünstig). Ersatz der Barytlösung durch Ringerlösung. Die Lunge ist zur Ausschaltung hydrostatischer Druckkräfte in Ringerlösung suspendiert. Von einem Niveaugefäß können durch Heben und Senken Füllung und Entleerung der Lunge vorgenommen werden. Schreibung der Volumänderung mit Aeroplethysmograph vom Luftraum des Niveaugefäßes, des Strömungsseitendruckes von der Trachea aus. Schreibung der statischen Dehnungskurve der Lunge und dynamischer Druckkurven bei verschiedener Strömungsgeschwindigkeit. Der Unterschied zwischen beiden gibt die dynamische Druckdifferenz zwischen Trachea und Alveolen. Aus der Volumkurve und Zeitmarkierung bestimmt sich die zugehörige Volumgeschwindigkeit.

verhältnisse besitzt wie die Kaninchenlunge, ist die Liefermenge V_1 der Menschenlunge in Litern das $\frac{40}{1000}$fache der Liefermenge V in Kubikzentimeter der Kaninchenlunge: $V_1 = \frac{40}{1000} \cdot V$ und $V = 25 \cdot V_1$. Für die intrapulmonären Luftwege der menschlichen Lunge ergibt sich die Strömungsgleichung:

$$p_{cm}\, H_2O = 0{,}18\, V_1 + 0{,}18 V_1^2 \quad (V_1 \text{ in Liter}).$$

Die aus anatomischen Daten berechnete Gleichung für die unteren Luftwege der Lunge des Menschen ist:

$$p_{cm}\, H_2O = 0{,}36 V_1 + 0{,}09 V_1^2.$$

In Anbetracht der Verschiedenheit des anatomischen Substrates ist die Abweichung keine übermäßig große.

2. Die dynamischen Widerstandskräfte in Lunge und Brustwand.

A. Trägheitskräfte.

Der Trägheitswiderstand ist abhängig von der bewegten Masse und der Beschleunigung.

Wenn bei maximaler Atmung (30 Atemzüge pro Sek.) die Zwerchfellverschiebung 6 cm pro Sek. beträgt und nach der raschen Biegung der Spirometerkurve angenommen wird, daß diese Geschwindigkeit in $^1/_{10}$ Sek. erreicht und am Schluß der Atemphase in dieser Zeit gebremst wird, ist die positive oder negative Beschleunigung 60 cm.

Bei einem Lebergewicht von 1500 g ist der Widerstand 90 000 dyn = ca. 90 g, welcher auf eine Zwerchfellfläche von ca. 300 qcm verteilt, eine durchschnittliche Belastung von 0,3 cm H_2O bedeutet. Auf der Lungenseite des Zwerchfells ist die Belastung nur ca. $^1/_3$ dieses Wertes, da das Gewicht beider Lungen etwa halb so groß wie das Lebergewicht ist und ihre Schwerpunktsverschiebung geringer ausfällt, indem nur die Basisfläche bewegt wird.

Die alveolären Druckdifferenzen, welche bei dieser maximalen Atmung durch die Strömungswiderstände in den Atemorganen bedingt werden, sind etwa 30mal größer.

Der Einfluß der Trägheitswiderstände ist bei der Atembewegung im allgemeinen von so geringer Größenordnung, daß er vernachlässigt werden kann. Immerhin ist es möglich, daß er bei maximaler Atmung den Verlauf der Kurve des Lungenoberflächendruckes (dynamischer Pleuradruck) in der Gegend des Phasenwechsels etwas beeinflußt.

B. Reibungswiderstand im Pleuraspaltraum.

Im Pleuraspaltraum findet bei der Lungenverschiebung eine Schichtströmung statt. Die Flüssigkeitsmenge im Pleuraraum ist zu wenigen Kubikzentimetern angegeben. Wenn wir 2 ccm in einer Pleuraseite rechnen, ist bei einer Lungenoberfläche von ca. 10 qdm die Flüssigkeitsschicht ca. 0,002 cm dick (d).

Wenn schematisch der Brustinhalt als Zylinder mit Radius $r = 10$ cm und Höhe $l = 20$ cm betrachtet wird, ist die an der Zwerchfellfläche $r^2\pi$ angreifende, den Strömungswiderstand überwindende Kraft

$$r^2 \cdot \pi \cdot p_{dyn} = 2\, r\pi \cdot l \cdot \frac{v}{d} \cdot \eta,$$

$$p_{cm}\, H_2O = \frac{2}{981} \cdot \frac{l}{r} \cdot \frac{v}{d} \cdot \eta.$$

(v = Verschiebungsgeschwindigkeit in cm/Sek., η für seröse Flüssigkeit wenig verschieden von Wasser, $\eta = 0{,}01$, $d = 0{,}002$ cm.)

Die Einsetzung der Werte gibt die Gleichung

$$p = \text{ca. } 0{,}02 \cdot v \text{ cm } H_2O.$$

Für die sehr hoch angesetzte Verschiebungsgeschwindigkeit bei maximaler Atmung von 6 cm/Sek. ist die Belastung des Zwerchfells ca. 0,1 cm H_2O, also von zu vernachlässigender Größenordnung.

C. Innere Reibungswiderstände in den deformierten Geweben.

1. Deformationswiderstand im Lungengewebe.

Wenn für eine Lunge der dynamische Oberflächendruck, die statische Elastizitätskurve und die Strömungsformel bekannt ist, ermittelt sich der Deformationswiderstand für verschiedene Strömungsgeschwindigkeiten aus der Gleichung (S. 110) zu:

$$p_{w\,pulm} = p_{pleur} + p_{el\,pulm} - p_{alv}.$$

Nach eigenen Versuchen zusammen mit WIRZ[1]) sind die Deformationswiderstände im Lungengewebe von gleicher Größenordnung wie die durch den Strömungswiderstand der Atemwege bedingten alveolären Druckdifferenzen. Ihre Zunahme mit wachsender Strömungsgeschwindigkeit folgt dagegen im Messungsbereich einer anderen Gesetzmäßigkeit:

$$p_w = a \cdot V - b \cdot V^2 = 0{,}0268\,V - 0{,}00011\,V^2 \quad (V \text{ in ccm/Sek.}).$$

Bei der Kaninchenlunge überwiegt bis Volumgeschwindigkeiten von 20 bis 40 ccm/Sek. der Anteil der Deformationswiderstände, für größere Volumgeschwindigkeiten der Strömungsdruck. Durch die Deformationswiderstände im Lungengewebe kann bei der Kaninchenlunge ein Bewegungswiderstand an der Lungenoberfläche bis $1^1/_2$ cm H_2O pro Flächeneinheit bedingt werden.

2. Summe der Deformationswiderstände von Lunge und Brustwand.

Bei passiver Ausatmung ist die bewegende Kraft die Summe der passiven Spannkräfte von Brusthöhleninhalt und Brusthöhlenwand: $\sum p_{el}$, welche in mittleren Dehnungslagen linear mit der Volumänderung (S. 101) abnimmt. Nach der Gleichung des dynamischen Kräftezusammenhanges (S. 108) ist für $p_{musk} = 0$

$$\sum p_{el} = p_{alv} + \sum p_w \quad \text{und} \quad \sum p_w = \sum p_{el} - p_{alv}.$$

Es wurde bei einer Versuchsperson nach Exspiration von $^1/_2$ Liter von maximaler Inspirationslage aus, entsprechend einer Dehnungslage von 0,8 Liter oberhalb der gewöhnlichen Ausatemlage, die Nasenöffnungen verschlossen und von der Mundhöhle aus der Pharynxdruck bei raschem Trommelgang graphisch registriert. Bei plötzlicher Freigabe der Nasenöffnungen wird der Verlauf der Strömungsseitendruckkurve im Pharynx geschrieben. Für dieselbe Versuchsperson war vorher das Strömungsdiagramm der Nasenhöhle bei Durchströmung von der Mundhöhle bestimmt worden: $p = a\,V + b\,V^2$ (S. 116). Aus der Seitendruckkurve im Pharynx wurde zunächst die zugehörige Volumgeschwindigkeitskurve abgeleitet, dann ihre Integralkurve, der Verlauf der Lungenvolumänderung, welcher die $\sum p_{el}$-Kurve parallel geht. Der Strömungsdruckanteil in den unteren Luftwegen wurde nach der Strömungsgleichung der Luftwege (S. 109) in Rechnung gesetzt.

Auch die Deformationswiderstände der Atemorgane des Menschen sind nach dieser Untersuchung von gleicher Größenordnung wie der Strömungsdruck der Atemwege. Ferner war auch hier eine Verlangsamung des Anwachsens des Deformationswiderstandes mit steigender Volumgeschwindigkeit festzustellen. (Diese Untersuchung fällt ca. 3 Jahre vor die Kaninchenarbeit. Der letztere Befund war so überraschend, daß ich in Anbetracht der vielen Fehlermöglichkeiten der Berechnung die Arbeit bis zu einer Nachkontrolle mit anderer Methode zurücklegte.) Für $V = {}^1/_4, {}^1/_2, {}^3/_4$ und 1 Liter waren die $\sum p_w$ Werte: 1,9, 2,9, 3,1 bzw. 2,3 cm H_2O. Bei $V = 1$ Liter ist $p_{alv} + \sum p_w = 3{,}9$ cm H_2O.

b) Die Veränderung der Druckwerte an verschiedenen Stellen der Atemorgane im Verlauf der Atembewegung.

Die spirometrische Kurve der Volumänderung der Atemorgane zeigt bei verschiedenen Atemverhältnissen im wesentlichen dieselbe Ablaufsform (S. 88), dagegen wechselt ihre Höhe (Atemtiefe) und die zeitliche Dauer eines Atemrhythmus (Frequenz). Die einzelnen Kräfte, welche bei der Atembewegung in Frage kommen, sind teils von der Dehnungslage abhängig ($p_{el\,thor}$ und $p_{el\,pulm}$), teils von der Volumgeschwindigkeit (p_{alv}, p_w). Die

[1]) WIRZ: Über Pleuradruck. Pflügers Arch. f. d. ges. Physiol. Bd. 199, S. 43. 1923.

ersteren Kräfte gehen in ihrer zeitlichen Änderung der Volumkurve parallel. Die letzteren Druckwerte sind vom Differentialquotienten der Volumkurve abhängig. Für die Pleuradruckkurve, welche einen Resultantenwert der elastischen, pneumatischen und dynamischen Widerstandskräfte darstellt, sind entsprechend mannigfaltige Verlaufsbedingungen gegeben.

1. Kurve der pneumatischen Druckänderung.

Eine Methode zur direkten Schreibung der respiratorischen Druckschwankung in der Lungenluft ist zur Zeit nicht vorhanden. Dagegen kann von verschiedenen Stellen der oberen Luftwege (Nasenöffnung [EWALD[1])], Pharynx, Trachea [GAD[2]), ARON, WIRZ[3])]) der Strömungsseitendruck geschrieben werden. Es wird angenommen [GAD[4])], daß der Druckanteil einer peripheren Strecke der oberen Luftwege zum Gesamtdruckgefälle in einem konstanten Verhältnis steht, die Druckschwankung an der Meßstelle also der Schwankung des Lungenluftdruckes in verkleinertem Maßstab parallel geht.

Diese Annahme ist nur in gewissen Grenzen zulässig, soweit es das lineare Glied der Strömungsformel $p = k_1 \cdot w_1 \cdot \eta \cdot V$ betrifft. Die Proportionalität wird gestört durch das quadratische Glied, den Anteil der Extrawiderstände $p = k_2 \cdot w_2 \cdot \gamma \cdot V^2$, da sie anders über die Luftwege verteilt sind als die Rohrwiderstände. Besonders bei hohen Strömungsgeschwindigkeiten sind daher Abweichungen zu erwarten.

Die *Strömungsdruckkurven* zerfallen in einen exspiratorischen Abschnitt, welcher über der Abszisse des Nulldruckes, und einen inspiratorischen Teil, welcher unterhalb liegt. Jedem Schenkel der Volumkurve (spirographische Kurve) entspricht also eine wellenförmige Erhebung oder Senkung der pneumatischen Druckkurve von der Nullabszisse aus und Rückbiegung zu ihr gegen Schluß der Atemphase. Wo die Volumkurve ihre äußersten Lagen erreicht (Phasenwechsel) schneidet die Druckkurve die Nullabszisse oder liegt in ihr, wenn es sich um eine Atempause handelt. Die größte Entfernung der Druckkurve von der Nullabszisse entspricht zeitlich der Stelle größter Steilheit der Volumkurve (Abweichungen siehe unten). Da der Druckwert jedoch nicht nur von der ersten, sondern auch von der zweiten Potenz des Differentialquotienten der Volumkurve abhängt, besteht keine reine Proportionalität zwischen Steilheit der Volumkurve und Ordinatenwert der Druckkurve.

Die noch von BORUTTAU[5]) zitierte Angabe GADS[6]), das Zeitintegral der Inspirations- und Exspirationszacke der Druckkurve müsse gleich groß sein (wenn die Volumänderung in beiden Phasen gleich ist), trifft daher nicht zu.

Der größte inspiratorische Ausschlag der Druckkurve ist bei ruhiger Atmung oft kleiner als der größte exspiratorische Ausschlag [GAD[7]), WIRZ[8])].

Auf die *Formenunterschiede* der Kurve in beiden Atemphasen und das Verhalten bei wechselnden Atembedingungen (ruhige Atmung, Röhrendyspnöe, Widerstandserhöhung, Vagotomie) hat vor allem WIRZ hingewiesen.

Bei gewöhnlicher Atmung werden die extremen Druckwerte meist in der ersten Hälfte jeder Phase erreicht, ein kürzerer, steilerer Anstieg biegt in einen horizontalen oder flach absinkenden Schenkel um (Abb. 31 a). Bei Röhrenatmung ist der initiale Gipfel ausgeprägter und wird früher erreicht. Erhöhter Strömungswiderstand bedingt längeres Andauern hoher Druckwerte (Kuppenform oder schief absinkendes Plateau) (Abb. 31 b). Bei Trachealverschluß wird die Kurve hyperbelähnlich (Abb. 31 c). Die Gipfel- und Plateaubildung ist oft im exspiratorischen Kurvenabschnitt ausgeprägter.

[1]) EWALD: Pflügers Arch. f. d. ges. Physiol. Bd. 19. 1879.
[2]) GAD: Arch. f. Physiol. 1879, S. 553.
[3]) WIRZ: Pflügers Arch. f. d. ges. Physiol. Bd. 199, S. 23. 1923.
[4]) GAD: Die Atemschwankungen des intrathorakalen Druckes. Arch. f. Physiol. 1878, S. 559.
[5]) BORUTTAU: Nagels Handb. d. Physiol. Bd. I, 1, S. 24. 1905.
[6]) GAD: Arch. f. Physiol. 1879, S. 553–558.
[7]) GAD: Arch. f. Physiol. 1878, S. 559.
[8]) WIRZ: Pflügers Arch. f. d. ges. Physiol. Bd. 199, S. 23. 1923.

Daß der Verlauf der pneumatischen Druckkurve mannigfaltigere Formen aufweist als die Volumkurve, ist zum Teil darauf zu beziehen, daß die Druckwerte eine doppelte Abhängigkeit vom Steilheitsgrad der Volumkurve besitzen. Durch das quadratische Glied gelangen anscheinend geringfügige Krümmungen der spirographischen Kurve hier zu deutlicher Ausprägung als Schwankungen der Drucklinie. Manche Erscheinungen, besonders die initiale Gipfelbildung, welche nicht immer der Stelle größter Steilheit der Volumkurve zeitlich entspricht, sind vielleicht durch den Widerstand der Massenträgheit des strömenden Mediums und des Schwimmers des volumregistrierenden Apparates bedingt.

2. Pleuradruckkurve.

Der dynamische Pleuradruck ist ein Summenwert. Die *Kurvenform* ist daher in weiten Grenzen je nach dem Anteil des elastischen Lungenzuges und der dynamischen Widerstandskräfte (p_{al}, p_w) verschieden. Je *langsamer* die

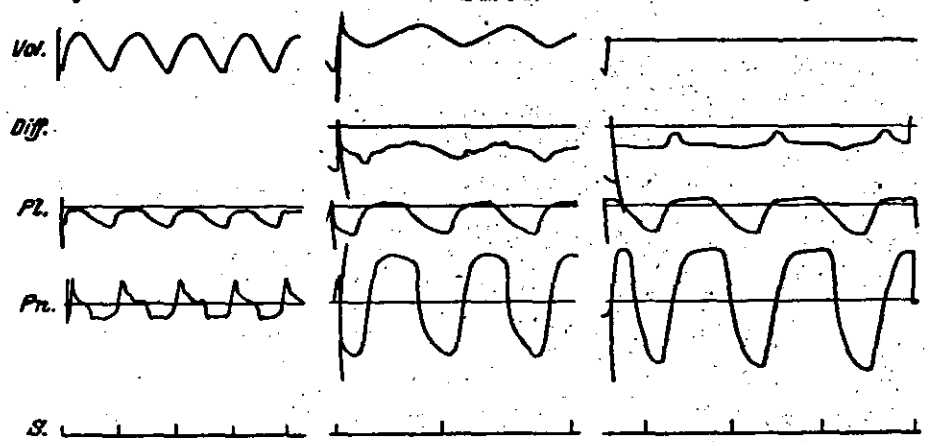

Abb. 31 a. Gewöhnliche Atmung.	Abb. 31 b. Peripherer Widerstand.	Abb. 31 c. Verschluß der Trachea.
Q = 13 ccm	Q = 10 ccm	Q = 0
n = 63	n = 66	n = 54
Vi = 27; Ve = 28	Vi = 30; Ve = 29	V = 0
L = 819 ccm	L = 860 ccm	L = 0

Q = Atemtiefe in ccm. n = Anzahl der Atemzüge pro Minute. V = Volumgeschwindigkeit in ccm/sec, Vi für Inspiration, Ve für Exspiration. L = Liefermenge pro Minute.

Vol. = Spirographische Kurve, Inspiration nach abwärts. *Pl.* = Pleuradruck. *Pn.* = Seitendruck in Trachea. *Diff.* = Differenzdruck zwischen Lungenoberfläche und Trachea.

Atmung ist, um so mehr nähert sich die Form der Pleuradruckkurve dem Typus der *spirographischen Kurve*. Je *rascher* die Bewegung, oder je größer die Bewegungswiderstände in den Luftwegen, um so ähnlicher wird die Pleuradruckkurve der *Strömungsdruckkurve*, um bei maximaler Zunahme des Bewegungswiderstandes (bei Trachealverschluß) fast vollständig mit ihr übereinzustimmen (Abb. 31 c).

Wenn man mit einer Druckdifferenzkapsel den Unterschied zwischen Pleuradruck und trachealem Seitendruck schreibt, also den peripheren Teil des Strömungsdruckes vom Pleuradruck abzieht, ist das Bild dieser Differenzkurve oft überraschend ähnlich der Volumkurve (Abb. 31 b).

Bei *ruhiger Atmung* entsprechen die tiefsten und höchsten Ausschläge der Pleuradruckkurve den Phasenwechselstellen. Der exspiratorische ansteigende Schenkel ist meist in einen ersten rascher sich hebenden und zweiten mehr horizontal verlaufenden Teil gegliedert. Der inspiratorische Schenkel ist schief absteigend, mit Andeutung einer Biegung zur Horizontalen vor dem Phasenwechsel. Bei *rascher oder erschwerter Atmung* liegt die höchste Erhebung der Kurve rückverschoben im exspiratorischen Teil, die tiefste Senkung im inspi-

ratorischen Teil. Die Phasenwechselstelle zur Inspiration verschiebt sich auf den absteigenden, diejenige zur Exspiration auf den aufsteigenden Schenkel. Im Verlauf der Exspiration kann deswegen der dynamische Pleuradruck vorübergehend positiv werden, ohne daß die Lunge kollabiert ist. Folgende Tabelle enthält einige am Kaninchen gemessene Durchschnittswerte. (Tab. 5.)

Tabelle 5.

Pleuradruck in cm H_2O	Gewöhnliche Atmung	Dyspnöe	Widerstand und Dyspnöe
Exspirationslage	− 0,8	+ 1,2	+ 2,7
Inspirationslage	− 7,3	− 9,4	− 12,6
Schwankungsbreite	6,5	10,6	15,3

Manche Formdetails der Strömungsdruckkurve finden sich wieder an der Pleuradruckkurve[1]).

3. Abdominaldruckkurve.

Die *respiratorischen Schwankungen des Abdominaldruckes* sind klein gegenüber den Änderungen des statischen Druckes im Abdomen bei Wechsel der Körperlage. Sie sind auch klein gegenüber der Schwankungsbreite des Pleuradruckes [$^1/_{40}$ bis $^1/_5$ derselben[2])]. Die aktive Arbeitsleistung bei der Zwerchfellkontraktion ist daher im wesentlichen nach Brusthöhlenseite hin gerichtet.

Vertiefung der Atmung verursacht parallel zur Steigerung der Pleuradruckschwankung oft auch eine Erhöhung der abdominellen Druckschwankung. Vergrößerung des Widerstandes in den Luftwegen bedingt meist kein der Zunahme der Pleuradruckänderung entsprechendes Wachsen der respiratorischen Druckänderung im Abdomen. Bei Trachealverschluß ist neben maximalen Pleuradruckschwankungen manchmal sogar eine Abnahme der Ausschlagsbreite der Bauchdruckkurve vorhanden.

Die Kurve des Abdominaldruckes ist nach Winkler[3]) wellenförmig, wobei die Gipfelpunkte verschieden zum Verlauf der Volumkurve liegen können. Winkler unterscheidet vier Typen, je nachdem die Kurve gleichsinnig oder ungleichsinnig der Volumkurve verläuft oder die Gipfelpunkte während den Phasen liegen. Bei eigenen Untersuchungen an Kaninchen und Katzen wurden ähnliche Formen gefunden, aber auch öfter mehrgipfelige Kurven. Ein inspiratorisches Steigen, exspiratorisches Sinken der Kurve weist nach Winkler auf ein passives Verhalten der Bauchdecken, der umgekehrte Verlauf auf aktive Exspiration hin. Es scheint wahrscheinlich, daß die verschiedenen Verlaufsformen auf ein zeitlich wechselndes Eingreifen abdomineller Exspirationsmuskeln und auf die Rückwirkung der Bewegungsvorgänge an der unteren Brustkorbapertur zurückzuführen sind.

c) Topographische Verhältnisse der Atemkräfte bei der Atembewegung.

1. Topographie des Luftströmungsvorganges in den Atemwegen.

A. Längsprofil der Strombahn.

Die Widerstände in den Luftwegen besitzen auf einem Längsprofil der Strombahn eine ungleichmäßige Verteilung, welche für die Rohrwiderstände und Extrawiderstände (S. 109) eine verschiedene ist[4]). (Tab. 6.)

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[1]) Arbeit Wirz: Über Pleuradruck. Pflügers Arch. f. d. ges. Physiol. Bd. 199, S. 26 bis 37. 1923; ferner Rohrer u. Wirz: Klin. Wochenschr. Jg. 2, Nr. 24. 1923.

[2]) Arbeit Nakasone: Über Abdominaldruck. Noch nicht publiziert.

[3]) Winkler: Beziehung zwischen Abdominaldruck und Respiration. Pflügers Arch. f. d. ges. Physiol. Bd. 98, S. 163. 1903.

[4]) Rohrer: Strömungswiderstand in den Atemwegen. Pflügers Arch. f. d. ges. Physiol. Bd. 162, S. 272. 1915.

Tabelle 6.

	Rohrwiderstände %	Extrawiderstände %
Obere Luftwege	54	89,1
Nase + Pharynx	52,06	22,2
Glottis	1,2	66,9
Trachea	0,74	—
Broncholobuläres System	46	10,9
Bronchialweg (Mittel)	13,4	10,15
Läppchen (Mittel)	32,6	0,75

Von den *Rohrwiderständen*, welche bei ruhiger Atmung den Hauptteil des Druckgefälles in den Luftwegen bedingen, ist etwa die Hälfte in den Nasengängen lokalisiert, die andere Hälfte im intrapulmonären Abschnitt, und zwar der größere Teil in den engen Bronchiolen der Läppchen.

Die *Extrawiderstände* sind zu $^9/_{10}$ in den oberen Luftwegen konzentriert. Die Glottisenge allein bedingt $^2/_3$, die Querschnittswechsel an der Nasenöffnung und zwischen Nase und Pharynx ca. $^1/_5$. Auf die unteren Luftwege fällt nur $^1/_{10}$.

Es erhellt sich daraus die atemphysiologische Bedeutung der drei Hauptstellen des Strömungswiderstandes als Orte, wo strömungsregulatorische Vorgänge erfolgen: Nasenflügelatmung, inspiratorische Erweiterung der *Stimmritze*, exspiratorische Verengerung. Die Inspirationsbewegung, welche gegen wachsende passive Spannungen erfolgt, wird durch diese *konkomittierenden Atembewegungen* erleichtert. Die Exspiration, für welche bei gewöhnlicher Atmung ein Überschuß an passiver Kraft vorhanden ist, wird dadurch gedämpft.

Ferner sind diese Stellen pathologisch-physiologisch Vorzugsorte von Strömungshindernissen (Stenosen der Nasengänge, Kehlkopfstenosen, Asthma bronchiale). (S. 127, Nachtrag 2.)

Der Strömungswiderstand in den *Nasengängen* ist individuell schwankend. Eine eigene Bestimmung des Strömungsdiagrammes der Nase mit Durchströmung von der Mundhöhle aus[1]) (Gebläsestrom, auf Volumwerte geeichte Vorschaltwiderstandsstrecke, Messung des Seitendruckes in der Mundhöhle) ergab für eine Person mit verengerten Nasengängen

$$p = 1{,}0\,V + 4{,}2\,V^2$$

gegenüber $p = 0{,}4\,V + 0{,}2\,V^2$ nach Berechnung für gewöhnliche Verhältnisse.

In der Nasenhöhle soll der Verlauf von Inspirations- und Exspirationsstrom verschieden liegen, der erstere höher ansteigen, der letztere mehr dem Boden der Nasenhöhle entlang gehen[2]).

Die Strömungsrichtung außerhalb der Nasenöffnung ist sicher verschieden. Bei Einatmung mehr zerstreut, bei Ausatmung, besonders wenn die Strömung schnell ist, strahlartig zusammengefaßt und abwärts gerichtet. Wenn bei beiden Atemphasen in der Nasenhöhle ein Unterschied des Stromverlaufes vorliegt, ist derselbe wahrscheinlich mit der Strömungsgeschwindigkeit wechselnd.

In der den Luftwegen vorgeschalteten engen Stelle, den Nasengängen, erfolgt die Anwärmung der Atemluft. Nach BLOCH[3]) wird $^5/_9$ der Temperaturdifferenz zur Außenluft hier ausgeglichen. Die Sättigung mit Wasserdampf findet nach MINK hauptsächlich im Pharynx statt[4]).

Topographische Verteilung der Strömungsgeschwindigkeit auf einem Längsprofil der Strombahn siehe S. 92.

B. Querprofil der Strombahn in den Lungen.

In der Lunge ist die Luftströmung in zahlreiche parallelgeschaltete Lüftungsbezirke aufgeteilt.

[1]) Ähnliche Bestimmungsverfahren KAISER: Arch. f. Laryngol. Bd. 3; ferner ZWAARDEMAKER: Untersuch. a. d. physiol. Lab. d. Univ. Utrecht 1909, S. 163.

[2]) MINK: Physiologie der oberen Luftwege. Leipzig: F. C. W. Vogel 1920, S. 16 u. 128. Die dort geschilderten Modellversuche sind nicht günstig gewählt.

[3]) BLOCH: Pathologie und Therapie der Mundatmung. Wiesbaden 1889. Ferner MINK: l. c. S. 67. Neue Untersuchung: LILJESTRAND u. SAHLSTEDT. Skand. Arch. f. Physiol. Bd. 46, S. 94. 1924.

[4]) MINK: l. c. S. 71.

Nach ROHRER[1]) ist der *Widerstand des Bronchialweges* zwischen Trachea und respiratorischen Lufträumen des Parenchyms für *periphere Läppchen doppelt so groß* wie für *zentrale Läppchen*. Der unregelmäßige Bau des Bronchialsystems bedingt zu *Beginn des Atemzuges* eine *ungleichmäßige Luftverteilung*, die zentralen Läppchen erhalten doppelt so große Liefermengen. Im *weiteren Verlauf* gleicht sich dieser Unterschied zunehmend aus (annähernd schon nach $^1/_2$ Sek.) und bildet sich eine *ungleiche Druckverteilung aus*. Die Druckdifferenz zwischen Alveolarluft und Bifurkation ist nach dieser Zeit für die peripherstenLobuli doppelt so groß wie für die zentralsten Läppchen.

Beim *Hustenstoß* ist zu Beginn die Entleerung der peripheren Lungenbezirke erschwert[2]). Da der Druck hier langsamer absinkt, findet durch inneren Druckausgleich im Lungengewebe eine vorübergehende Überdehnung des peripheren Parenchyms statt[3]): (*Kreuzfuchs-Phänomen*, am Röntgenschirm Aufhellung der Lungenspitze beim Husten).

Bei hohen Druckdifferenzen zwischen Parenchym und Bronchen findet *inspiratorisch eine Querschnittsvergrößerung, exspiratorisch eine Kompression der Bronchen* statt. (Exspiratorische Dyspnöe bei Stenosen in den unteren Luftwegen: Asthma bronchiale. Nach eigener subjektiver Beobachtung ist im Asthmaanfall oft die Exspiration für kurze Zeit nach dem Phasenwechsel nicht erschwert, um dann plötzlich, mit dem Einsetzen der komprimierenden Wirkung des Überdruckes im Parenchym stark gehemmt zu werden.)

Zwischen größeren Lungenabschnitten, besonders zwischen den *Lungenlappen*, bestehen *keine merklichen Unterschiede der Strömungsbedingungen*[4]). Die Dehnungsänderung aller Lungenlappen ist eine gleichmäßige (Ausnahmen bei tiefer Atmung, siehe S. 100).

Die Aspiration von Fremdkörpern oder Flüssigkeiten hauptsächlich in die unteren Abschnitte des Bronchialsystems kann nicht als Beweis für eine überwiegende Beatmung der Unterlappen aufgefaßt werden. Das spezifische Gewicht und die Bewegungsinercie dieser Massen ist sehr verschieden von der bewegten Atemluft. In aufrechter Körperhaltung bedingen beide Ursachen, im Liegen die letztere, notwendig eine Bevorzugung der Unterlappenbronchen, auch bei gleichgroßer Atemtätigkeit aller Lungenabschnitte.

Ein verschiedenes Verhalten des peripheren Parenchyms kann dynamisch entstehen, wenn der Lungendruck hoch ist und der höhere Ausströmungswiderstand die Entleerung der Läppchen mit langem Bronchialweg hindert. Es kann wie beim Hustenstoß eine *exspiratorische vorübergehende Überdehnung peripherer Lungenteile* entstehen, welche röntgenologisch an der Lungenspitze zu beobachten ist, besonders unter Verhältnissen, wo der Strömungswiderstand in den Bronchen noch erhöht ist (Asthma, Emphysembronchitis). Es handelt sich dabei jedoch nicht um eine Aufblähung der Oberlappen von den Unterlappen her[5]), sondern die *Erscheinung kommt durch inneren Spannungsausgleich im Parenchym zustande*[6]). Die Entleerung der peripheren Lungenteile wird durch die exspiratorische Kompression der Bronchen noch ungünstiger gestaltet.

Die verschieden langen Bronchialwege zu peripheren und zentralen Lungenteilen bedingen inspiratorisch auch eine verschieden rasche Auswaschung des *schädlichen Raumes* der zuführenden Atemwege. Etwa $^1/_3$ des schädlichen Raumes liegt peripher von den Abzweigungsstellen der zentralsten Läppchen. Die ungleiche Geschwindigkeitsverteilung auf dem Strömungsquerschnitt (die Geschwindigkeit in der Achse der Strombahn ist doppelt

[1]) ROHRER: Strömungswiderstand in den Atemwegen und Einfluß der unregelmäßigen Verzweigungen des Bronchialsystems auf den Atmungsverlauf in verschiedenen Lungenbezirken. Pflügers Arch. f. d. ges. Physiol. Bd. 162, S. 281. 1915.

[2]) ROHRER: l. c. S. 274.

[3]) ROHRER: Topographische Verteilung der Luftströmung in der Lunge. Schweiz. med. Wochenschr. 1921, Nr. 32. Dort Beschreibung eines Modellversuchs.

[4]) ROHRER: Pflügers Arch. f. d. ges. Physiol. Bd. 162, S. 263. 1915.

[5]) KREUZFUCHS: Antagonismus der Atmung der Spitzen und der basalen Anteile der Lungen. Wien. klin. Wochenschr. Jg. 32, Nr. 24, S. 635.

[6]) ROHRER: Topographie der Luftströmungsverhältnisse in den Lungen. Schweiz. med. Wochenschr. 1921, Nr. 32. Ferner: Über Lungenemphysem. Münch. med. Wochenschr. 1916, Nr. 34, S. 1219.

so groß wie die mittlere Geschwindigkeit) bedingt ferner einen Unterschied zwischen physiologischer und anatomischer Größe des schädlichen Raumes. Schon bei geringerer Atemtiefe, als dem Inhalt der zuführenden Luftwege entspricht, gelangt Außenluft in die Alveolen. Eine vollständige Auswaschung der Randpartien der Strombahn kommt dagegen erst bei tiefen Atemzügen zustande[1]).

2. Topographie des Pleuradruckes.

Bei eigenen Untersuchungen am Kaninchen mit vergleichender Messung des Druckes von 2 bis 4 verschiedenen Lungenoberflächenorten, konnten, bei in weitem Umfang veränderten Atemverhältnissen, *keine Unterschiede des dynamischen Pleuradruckes an verschiedenen Stellen* gefunden werden[2]).

3. Topographie der respiratorischen Druckschwankungen im Abdomen.

Im *Abdomen bestehen Unterschiede der respiratorischen Druckschwankungen* an verschiedenen Stellen, nicht hinsichtlich des Kurvenverlaufes, aber in der Schwankungsbreite. In Rückenlage ist beim Kaninchen nach eigenen Untersuchungen die Druckschwankung epigastrisch am größten, sie nimmt caudalwärts ab bis zur Hälfte im unteren Bauchraum. In senkrechter Körperlage, Kopf nach oben, wurden die Druckschwankungen umgekehrt unten am größten gefunden. (Tab. 7.)

Tabelle 7.

Respiratorische Abdom. Druckschw.	Rückenlage	Senkrechte Lage
Epigastrisch	0,75 cm H_2O	0,85 cm H_2O
Mesogastrisch	0,5 „ „	1,5 „ „
Hypogastrisch	0,35 „ „	1,7 „ „

d) Dynamische Verhältnisse der Körperhöhlen bei veränderten mechanischen Bedingungen.

1. Einlagerung fremder Medien.

Lufteinlagerung in den *Pleuraspaltraum* verschiebt das Niveau der Pleuradruckkurve in der Richtung positiver Druckwerte, ohne die respiratorische Druckschwankung wesentlich zu beeinflussen, solange nicht Lungenkollaps eintritt[3]).

Lufteinlagerung ins *Abdomen* erhöht das Niveau des Abdominaldruckes, ohne die respiratorischen Schwankungen eindeutig zu verändern (Luftfüllung bis 300 ccm beim Kaninchen). Unmittelbar nach der Einfüllung wird der Druck am größten gefunden, um dann langsam zu sinken, was wahrscheinlich als Anpassung des Bauchmuskeltonus an das erhöhte Bauchhöhlenvolumen zu deuten ist. Lufteinblasung in den Magen bedingt ähnliche Verhältnisse[4]).

2. Ausbreitung äußerer und innerer Druckschwankungen in den Körperhöhlen.

Äußere Druckschwankungen (Thoraxkompression) bereiten sich, nach eigenen Untersuchungen am Kaninchen, im Brustraum rasch und gleichmäßig aus[5]). Druckschwankungen von der Trachea her erleiden eine Verzögerung, entsprechend dem Strömungsausgleich mit der Lungenluft.

[1]) Rohrer: Pflügers Arch. f. d. ges. Physiol. Bd. 162, S. 293. 1915 u. Bd. 164, S. 295. 1916.
[2]) Arbeit Wirz: Pflügers Arch. f. d. ges. Physiol. Bd. 199, S. 45. 1923.
[3]) Arbeit Wirz: Über Pleuradruck. Pflügers Arch. f. d. ges. Physiol. Bd. 199, S. 34. 1923.
[4]) Arbeit Nakasone: Über Abdominaldruck. Noch nicht publiziert.
[5]) Arbeit Wirz: l. c. S. 39.

Im *Abdomen* ist *der Druckausgleich kein vollständiger. Lokale Druckschwankungen* durch eine rasche oder langsame leichte Kompression an einer beschränkten Stelle der Bauchwand pflanzen sich zwar ohne merkliche Zeitdifferenz auf den übrigen Bauchraum fort, erleiden aber *mit wachsender Entfernung vom Druckort* eine *Abnahme der Schwankungsgröße*[1]). Bei Kompression an größeren Flächen ist die Abnahme geringer. Ebenso breiten sich stärkere Druckschwankungen gleichmäßiger aus. Die bei der Atmung bewegten Wandungsabschnitte des Abdomens sind zwar ziemlich ausgedehnt, aber trotzdem bestehen Unterschiede der respiratorischen Druckschwankung an verschiedenen Stellen im Bauchraum, besonders wenn das mittlere Niveau des Abdominaldruckes klein ist und die Schwankung gering ist. *Vor allem wichtig erscheint das Druckniveau.* Bei schlaffen Bauchdecken stellt der Bauchinhalt im Liegen gleichsam einen lose geschichteten Haufen von Organen dar, wo eine lokale Verschiebung im wesentlichen eine lokale Druckänderung in der nächsten Umgebung bedingt. Durch einen strafferen Wandungstonus wird der Inhalt zu einer Einheit zusammengefaßt, Druckschwankungen breiten sich auf den ganzen Bauchinhalt aus (z. B. meteoristisches Abdomen.) Die Verhältnisse sind vergleichbar der verschiedenen Dämpfung der Pulswelle in der Peripherie bei schlaffen oder gespannten Gefäßwänden.

Zwischen *Brusthöhle und Bauchraum* findet eine *gegenseitige Übertragung rascher Druckschwankungen* statt, welche aber durch das Zwerchfell eine starke Dämpfung erfährt. Bei Thorax- oder Bauchkompression erscheinen parallele Zacken an der Pleuradruck- und Abdominaldruckkurve. Die Übertragung ist jedoch keine quantitative. Nach doppelseitiger Phrenicotomie ist die Übertragung rascher Druckänderungen annähernd quantitativ. Die Körperhöhlen sind gegenseitig ihren Druckschwankungen schutzlos preisgegeben.

3. Künstliche Atmung.

Bei denjenigen Beatmungsmethoden, welche nicht einen direkten Ersatz des Lungenluftwechsels (Meltzer) anstreben, sondern dieses Ziel durch einen Ersatz der Atembewegung verfolgen, gelangen entweder *äußere Krafteinwirkungen auf die Körperwand* oder *innere pneumatische Druckschwankungen* zur Anwendung.

Das erstere Vorgehen ist eine Nachahmung der Wirkung inspiratorischer und exspiratorischer Muskelkräfte: *Silvester, Schaefer, Schultzesche Schwingungen, Inhabad-Apparat.* Die Atembewegung verläuft in physiologischer Richtung. Die Lungendehnungsänderung wird passiv durch eine Körperwandbewegung herbeigeführt.

Bei der *Beatmung von der Lunge her* wird der Brusthöhleninhalt der führende Abschnitt, welcher die Körperwandbewegung von innen her mittelbar verursacht.

Künstliche Atmung von der Brustwand her ist hauptsächlich wirksam als *Kompression der Brusthöhle*: Verschiebung der Dehnungslage in exspiratorischer Richtung, unterhalb die passive Ruhelage. Die Inspiration erfolgt durch die in dieser Stellung inspiratorisch wirkenden passiven Atemkräfte.

Versuche an lebenden Menschen[2]) ergaben bei Apnöe viel kleinere Ventilationsgrößen als ohne Apnöe (unbewußtes Mitatmen).

Die Bewegungen der Arme vermehren die Ventilation in unbedeutendem Grade. Die Atemtiefe ist beim Apnoischen vom angewandten Kompressionsdruck abhängig. Manuelle Silvester-Atmung bedingt eine Atemtiefe von ca. 0,19 Liter, Schäfer-Atmung 0,17 Liter, maschinelle Atmung (Apparat von Fries) 0,22 Liter. Die Minutenleistung steigt mit der Frequenz, bei 15—20 Atemzügen werden 3—4 Liter pro Minute erreicht. Die Dehnungslage ist in exspiratorischer Richtung verschoben.

Eine eigene *vergleichende Untersuchung* an 3 Hunden über *Silvester* (*S*), *Inhabad* (*J*) und *Pulmotor* (*P*) Beatmung, mit Schreibung von *trachealem Seitendruck, Pleuradruck* (bei einem Tier auch *Abdominaldruck, Carotidendruck* und *Jugularvenendruck*) ergab hinsichtlich des *Pleuradruckes* bei *S* und *J* meist höhere Druckschwankungen im Pleuraraum gegenüber *P*. Die *S*- und *J*-Kurven sind in positiver Druckrichtung verschoben, oft mehr als zur Hälfte über der Nullabszisse liegend (Verschiebung der Dehnungslage in exspiratorischer Richtung). Die Pleuradruckkurve von *P* liegt meist vollständig unter der Nullabszisse, etwa um dieselbe Mittellage schwankend, wie die Kurve bei spontaner, ruhiger Atmung, aber etwas weiter nach unten und oben ausschlagend. Die Kurve des intrathorakalen Druckes

[1]) Eigene Beobachtungen an Kaninchen und Katzen, mit gleichzeitiger Druckschreibung von drei bis vier Stellen des Bauchraumes.

[2]) Liljestrand, Wollin u. Nilsson: Ventilation bei künstlicher Atmung. Skandinav. Arch. f. Physiol. Bd. 29, S. 149. 1913. Dort Literatur.

besitzt bei *P* eine Phasenumkehr gegenüber der Spontanatmung: inspiratorische Hebung, exspiratorische Senkung, bedingt durch die Umkehr der pneumatischen Druckverhältnisse in der Lunge. Die *abdominellen* Druckschwankungen sind bei *P* kleiner oder gleich wie bei ruhiger Spontanatmung, bei *S* und besonders bei *J* vergrößert.

S und *J* bewirken am toten Tier Druckschwankungen in Carotis und Jugularvene (Schreibung von Seitenast aus: V. facialis). Der Venendruck steigt: Stauung. Diese Wirkung auch am lebenden Tier. *P* bedingt kaum deutliche Druckschwankungen in den Gefäßen außerhalb des Thorax; aber auch am toten und am lebenden Tier keine Änderung des Venendruckniveaus. BRUNS findet hinsichtlich des Einflusses auf das Niveau des Venendruckes bei *J* und *P* entgegengesetzten Befund[1]).

e) Einfluß der dynamischen Verhältnisse auf die Dehnungslage und den Ablauf der Atembewegung.

Bei *ruhiger Atmung* treten die dynamischen Widerstandskräfte gegenüber den Änderungen statischer Kräfte zurück.

Ruhige Einatmung ($^1/_2$ Liter) von der Gleichgewichtslage aus bedingt ein Anwachsen der Spannungsresultanten $\sum p_{el}$ von Lunge und Brustwand von 0 auf 7 cm H_2O (S. 101). Die Strömungsdruckdifferenz in der Lungenluft ist ca. $^1/_2$ cm H_2O, die Deformationswiderstände $\sum p_w$ sind wahrscheinlich von ähnlicher Größenordnung.

Die inspiratorische Muskelarbeit hat also hauptsächlich passive statische Kräfte zu überwinden. Die gesteigerte Spannungs- und Lageenergie ist mehr als genügend, um die Bewegungswiderstände der exspiratorischen Phase zu überwinden (S. 87 u. 89).

Dehnungslage und Bewegungsverlauf der ruhigen Atmung ist daher im wesentlichen durch das Verhältnis des Zusammenarbeitens von muskulären und passiven statischen Kräften bestimmt. Die Dehnungsrichtung mit geringster Spannungszunahme ist bevorzugt (S. 103).

Je *höher die Bewegungsgeschwindigkeit* steigt, oder je größer die *Bewegungswiderstände* werden (z. B. Stenosen), *um so mehr gewinnen die dynamischen Kräfte Einfluß auf Dehnungslage und Atemverlauf.* Mit zunehmender Respirationsfrequenz vermindert sich die erreichbare Atemtiefe und die erreichbare Minutenleistung (S. 79).

Der abdominelle Atemtypus tritt bei beschleunigter Atmung zurück gegenüber der thorakalen Bewegungsrichtung, bei welcher geringere Massenkräfte zu überwinden sind.

Erhöhte Bewegungswiderstände bedingen eine Veränderung des Atemtypus, Beiziehung von Hilfsmuskeln in der Einatmungsphase und eventuell auch Ausatemphase (S. 90). Ferner findet besonders bei intrapulmonärer Verengerungen der Strombahn, welche exspiratorisch sich verstärken (S. 117), eine *Rückwirkung auf die Dehnungslage* statt. Die Ausatemlage verschiebt sich entsprechend der erschwerten Entleerung der Lungen in inspiratorischer Richtung. Die Atemexkursion rückt automatisch in eine Zone, wo größere passive Spannungskräfte für die Ausatmung verfügbar sind. (EINTHOVEN: Pflügers Archiv Bd. 51.)

Die *Bewegungswiderstände* beeinflussen den Bewegungsablauf nicht nur unmittelbar mechanisch, sondern *wahrscheinlich auch reflektorisch*, auf dem Wege proprioceptiver Bahnen der Körperwand, speziell der Atemmuskeln. Normalerweise besteht keine deutliche bewußte Empfindung eines Atemwiderstandes. Das Gefühl der Atemnot bei erschwerter Atmung enthält dagegen neben dem Drang nach Luft auch die Wahrnehmung eines Bewegungswiderstandes (z. B. im Asthmaanfall).

VI. Energetik der Atmung.

Die Atembewegung wird durch Muskelarbeit geleistet. Bei ruhiger Atmung erfolgt nur eine Atemphase unmittelbar durch Muskelzug. Die exspiratorische Phase wird durch in der ersten Bewegungsrichtung erzeugte Lage- und Spannungsenergie veranlaßt und bedingt keine Muskelarbeit, oder, wenn sie durch Muskelzug gebremst ist, nur geringfügige statische Muskelarbeit. Bei rascher oder erschwerter Atmung können auch beide Bewegungsrichtungen aktive Muskeltätigkeit erfordern.

[1]) Zentralbl. f. Chirurg. 1923, S. 738 und Vox med. II, Nr. 12. 1922.

a) Bestimmung der Atemarbeit.

1. Indirekte Bestimmung aus dem Stoffwechsel.

Wie jede Muskelarbeit kann die Atemarbeit aus der Stoffwechseländerung bei einer Änderung der Atemleistung indirekt bestimmt werden.

Bei *willkürlich gesteigerter Atmung* ist die *pro Liter Mehrventilation* in der Minute gefundene Zunahme des O_2-Verbrauches wechselnd zwischen 2 bis 10 ccm O_2 pro Minute [SPECK, ZUNTZ und HAGEMANN, A. LÖWY, ZUNTZ und SCHUMBURG, LILJESTRAND[1])].

Bei *Steigerung der Atmung durch Vergrößerung des schädlichen Raumes* (Röhrenatmung) bestimmt LILJESTRAND[1]) wesentlich kleinere Werte: 0,3 bis 0,7 ccm O_2 pro Liter Mehrventilation. Die Größe ist abhängig von der Atemfrequenz: für 10 bzw. 15, bzw. 20 Atemzüge pro Minute: 0,66, 0,26 und 0,56 ccm O_2 pro Liter Ventilation.

Mit steigender Ventilation wächst der O_2-Verbrauch zunehmend rascher, nach Art einer *parabolischen Kurve*, welche je nach der Atemfrequenz verschieden rasch ansteigt. Bei Ventilation bis 20 Liter pro Minute sind Frequenzen zwischen 10—30 pro Minute günstig, bei steigender Ventilation ist Frequenz 20 am vorteilhaftesten, bei sehr großer Ventilation Frequenz 30[2]).

Willkürliche Steigerung der Atmung bedingt eine abnorme Anstrengung in der Exspirationsphase, ferner Nebenbewegungen, welche die Stoffwechselzunahme mit beeinflussen[3]).

Die Atemsteigerung bedingt zudem nicht nur eine Zunahme der mechanischen Atemarbeit, sondern auch eine erhöhte Wärmeabgabe (Erwärmung der Atemluft, Sättigung mit Wasserdampf). Es ist nicht unwahrscheinlich, daß auch die Messungen von LILJESTRAND, welche für die ruhige Atmung einen Stoffwechselanteil von 1—3,5% des Ruhestoffwechsels ergeben (gegenüber 10—15% früherer Bestimmungen), noch zu hohe Werte darstellen.

Wichtig ist die Feststellung, daß die *Atemarbeit mit dem Minutenvolum steigt*, aber nicht proportional, sondern rascher, daß ferner *bei gleicher Minutenleistung auch die Frequenz Einfluß* besitzt. Niedere Frequenz mit großer Atemtiefe bedingt vermehrte Atemarbeit [LILJESTRAND, ferner REACH und ROEDER[4])].

2. Bestimmung der Abhängigkeit der Atemleistung von wechselnden Umständen.

A. Volumleistung.

Bei maximaler Atemanstrengung und wechselnder, willkürlich eingehaltener Atemfrequenz ist die Minutenleistung zwischen 20—30 Atemzügen pro Minute ein Maximum. Sie ist geringer bei niedrigeren oder höheren Frequenzen (S. 79). Nach der Untersuchung an weiteren drei Versuchspersonen liegt die günstigste Frequenzzone individuell etwas verschieden. Einschaltung von äußeren Atemwiderständen verringert die Volumleistung und verschiebt die optimale Frequenz zu niedrigeren Werten.

B. Äußere Arbeitsleistung.

Bei Atmung durch Röhren verschiedenen Widerstandes und gleichbleibender Atemfrequenz ist die äußere Strömungsarbeitsleistung für eine bestimmte Größenzone des äußeren Widerstandes ein Maximum. Dieser Höchstwert liegt für 24 Atemzüge pro Minute bei einer durch äußeren Widerstand bedingten Druckhöhe von 60—70 cm H_2O, entsprechend etwa der Hälfte des maximalen Atemdruckes. Die größte äußere Arbeitsleistung in einer Strömungsrichtung war ca. 30 mkg pro Minute[5]).

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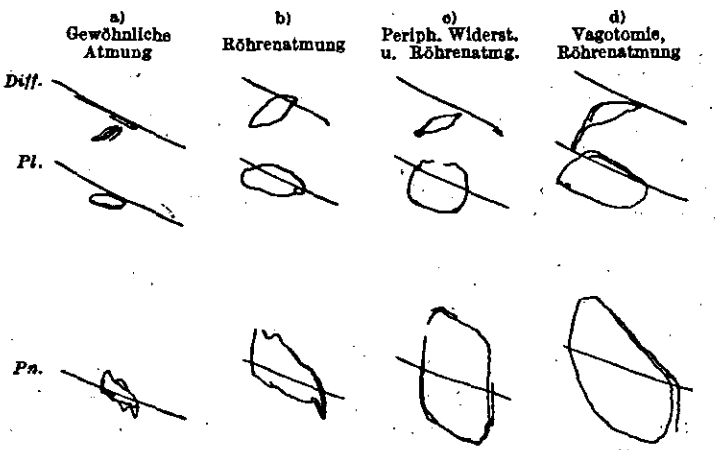
[1]) LILJESTRAND: Untersuchungen über die Atmungsarbeit. Skandinav. Arch. f. Physiol. Bd. 35, S. 199. 1917. Dort Literatur.
[2]) LILJESTRAND: l. c. S. 246.
[3]) LILJESTRAND: l. c. S. 250 u. S. 275.
[4]) REACH u. ROEDER: Biochem. Zeitschr. Bd. 22, S. 471. 1909.
[5]) ROHRER: Schweiz. med. Wochenschr. 1921, Nr. 41.

3. Messung der mechanischen Atemarbeit in den Atemorganen.

Die Atembewegung ist eine Volumänderung dQ, welche im Zeitelement dt gegen die in diesem Zeitpunkt vorhandene widerstehende Kraft p erfolgt. Die Arbeitsleistung im Zeitelement dt ist:

$$dA = p \cdot dQ, \qquad p = f(t).$$

Wenn am Volum registrierenden Apparat eine Schreibfläche sich mit dem Schwimmer bewegt und senkrecht zur Bewegungsrichtung die Druckwerte von irgendeiner Stelle der Atemorgane (Trachea, Pleuradruck, Differenzdruck zwischen Trachea und Lungenoberfläche) während eines Atemzyklus geschrieben werden, erhält man ein *Diagramm der Arbeitsleistung* am betreffenden Ort des Atemsystems während eines Atemzyklus [ROHRER und WIRZ, Bestimmungen am Kaninchen[1])]. *Flächengröße* und *Form der Arbeitsdiagramme* sind veränderlich, je nach Meßstelle, Atemtiefe, Volumgeschwindigkeit und Strömungswiderstand in den Atemwegen (Abb. 32a, b, c, d).



	a)	b)	c)	d)
Q ccm	25	47	44	69
V ccm	55	102	64	65
Arb. g/cm Pleuradruck	63	287	510	709
Arb. g/cm Trach.-Dr.	42	184	481	611
Arb. g/cm *Diff.-Dr*	7	100	51	104

Abb. 32. Arbeitsdiagramme.

Es wird möglich sein, mit dieser Methode bei Ausschaltung der aktiven Atemkräfte (curarisiertes Versuchstier) und passiver Beatmung, durch pneumatischen Druck von den Luftwegen her, die Größe der in den Atmungsorganen geleisteten Gesamtarbeit bei verschiedenem Minutenvolumen, wechselnder Frequenz und Atemtiefe systematisch festzustellen.

4. Berechnung der mechanischen Atemarbeit.

Bei ruhiger Atmung wird nur inspiratorisch muskuläre Arbeit geleistet. Es soll schematisierend angenommen werden, daß Inspiration und Exspiration gleich lange dauern und mit konstanter Geschwindigkeit erfolgen. Es sei die Atemtiefe Q Liter, die Frequenz pro Minute n. Das inspirierte Minutenvolum ist $L = n \cdot Q$, die Volumgeschwindigkeit V bei einer Strömungszeit von 30 Sek.: $V = \frac{L}{30}$.

A. Elastische Spannungsarbeit.

Bei der Einatmung von Q Litern von gewöhnlicher Einatemstellung aus wächst die Spannung von 0 bis $k_{el} \cdot Q$ cm H_2O (S. 101), $k_{el} = 14$ cm H_2O.

[1]) WIRZ: Pflügers Arch. f. d. ges. Physiol. Bd. 199, S. 47. 1923. Ferner ROHRER u. WIRZ: Klin. Wochenschr. Jg. 2. Nr. 21.

Es ist die Arbeitsleistung für eine Inspiration:

$$A_Q = \frac{1}{2} \cdot k_{el} Q \cdot Q = \frac{k_{el}}{2} \cdot Q^2 .$$

Die Arbeit für n Atemzüge:

$$A_L = n \cdot \frac{k_{el}}{2} \cdot Q^2 = n \cdot \frac{k_{el}}{2} \cdot \frac{L^2}{n^2} = \frac{k_{el}}{2} \cdot L^2 \cdot \frac{1}{n} .$$

B. Dynamische Widerstände.

Der Strömungswiderstand ist (S. 109):

$$p_{als} = a_1 V + b_1 V^2 ,$$

die Deformationswiderstände (S. 112):

$$p_w = a_2 V - b_2 V^2 .$$

Es soll angenommen werden, daß sich die quadratischen Glieder aufheben. Es sei

$$p_{als} + p_w = k_w \cdot V \quad (k_w = a_1 + a_2) .$$

Nach Bestimmung an der Lunge[1]) ist $a_2 =$ ca. $4 \cdot a_1$.

Es sei angenommen, zwischen dem Deformationswiderstand in den ganzen Atemorganen und Strömungswiderstand in den ganzen Lungenwegen bestehe dasselbe Verhältnis, wie für die Lunge allein. Für die Atemwege des Menschen ist $a_1 = 0{,}8$ und $k_w = a_1 + a_2 = 5\,a_1 = 4$. Für $V = 1$ Liter pro Sek. ist bei dieser Größe von k_w: $p_{als} + p_w = 4$ cm H_2O, entsprechend dem S. 112 bestimmten Wert 3,9 cm H_2O.

Die dynamische Arbeitsleistung ist, da gegen den Widerstand $(p_{als} + p_w)$ das Volumen L transportiert wird:

$$A = (p_{als} + p_w) L$$

da

$$(p_{als} + p_w) = k_w \cdot V \quad \text{und} \quad V = \frac{L}{30} ,$$

ist

$$A = \frac{k_w}{30} \cdot L^2 .$$

C. Gesamtarbeit der Inspiration pro Minute.

Die Summe der elastischen Spannungsarbeit und dynamischen Arbeitsleistung ist

$$A = \frac{k_{el}}{2} \cdot L^2 \cdot \frac{1}{n} + \frac{k_w}{30} \cdot L^2 = \left(\frac{k_{el}}{2} \cdot \frac{1}{n} + \frac{k_w}{30} \right) \cdot L^2 .$$

Der Bau dieser Formel stimmt überein mit den Ergebnissen der Stoffwechseluntersuchungen. Die Atemarbeit nimmt nicht proportional, sondern in Form einer Parabel zu, mit dem Minutenvolum. Sie steigt ferner mit der Atemtiefe $\left(\frac{1}{n}\right)$.

Da die Druckwerte in cm H_2O und die Volumwerte in Litern gemessen sind, ist $A = 0{,}01 \cdot p \cdot L$ mkg.

Bei $k_{el} = 14$ und $k_w = 4$ hat der Ausdruck $\left(\frac{k_{el}}{2} \cdot \frac{1}{n} + \frac{k_w}{30}\right)$ für verschiedene Frequenzen die Werte:

Tabelle 8.

Frequenz pro Minute . .	5,1	8,1	11,3	15	19	26
$\left(\frac{k_{el}}{2} \cdot \frac{1}{n} + \frac{k_w}{30}\right)$	1,5	1,0	0,75	0,6	0,5	0,4

Ein Anstieg der Frequenz von 5 auf 11 bedingt ein Sinken der Atemarbeit auf etwa die Hälfte. Mit weiterem Steigen der Frequenz verlangsamt sich die Abnahme der Arbeit.

Bei ruhiger Atmung und einem Minutenvolum von 7 Litern ist die Atemarbeit pro Minute bei 15 Atemzügen nur 0,3 mkg, entsprechend etwa $^1/_2$ ccm O_2 (1 mkg = 1,5 ccm O_2)[2]).

[1]) Wirz: Pflügers Arch. f. d. ges. Physiol. Bd. 199, S. 43. 1923. $a_1 = 0{,}0072$, $a_2 = 0{,}0268$.

[2]) Du Bois-Reymond, R.: Ergebn. d. Physiol. Jg. I, 2, S. 402.

Für verschiedene Minutenvolumina und 15 Atemzügen pro Minute sind die O_2-Gaswechselzunahmen (Tab. 9):

Tabelle 9.

O_2-Gaswechselzunahme ccm/Min.	15 Liter/Min.	22,5 Liter/Min.	30 Liter/Min.
Nach Formel	2,0 ccm	4,4 ccm	8,1 ccm O_2 pro Min.
Nach LILJESTRAND[1]).	9,5 „	21 „	43 „ „ „ „

Die Werte sind also etwa $^1/_5$ der nach der Stoffwechselmethode bestimmten. Es ist nicht unwahrscheinlich, daß diese letzteren Werte infolge der Erhöhung der Wärmeabgabe zu groß sind. Andererseits sind für die Ableitung der Formel manche Verhältnisse schematisiert und ist die Festsetzung von k_w nicht sehr zuverlässig[2]).

Für $\frac{k_w}{30} > \frac{k_{el}}{2} \cdot \frac{1}{n}$ ist die Arbeit für die Überwindung dynamischer Widerstände größer als die elastische Spannungsarbeit. Es müssen oberhalb der Grenze von 50 Atemzügen pro Minute unter allen Umständen aktive exspiratorische Kräfte mitwirken, da die inspiratorisch gespeicherte potentielle Energie nicht mehr für die Leistung der exspiratorischen Arbeit ausreicht. Tatsächlich findet das Eingreifen von exspiratorischen Muskeln schon bei niedrigeren Frequenzen statt, da die verfügbare Ausatemzeit mit steigender Frequenz immer kürzer wird. (Eine genaue Berücksichtigung der Verhältnisse der passiven Ausatmung bei verschiedener Frequenz wird durch die Anwendung der Theorie aperiodisch gedämpfter Schwingungen auf den Exspirationsvorgang möglich sein.)

b) Rückwirkung der Atemarbeit auf den Verlauf der Atembewegung.

ROHRER hat die Arbeitshypothese aufgestellt, daß die *Größe der Atemarbeit für die Regulation der Atemfrequenz maßgebend* ist[3]).

Von einem Atemzug von der Tiefe Q geht für den Lungenluftwechsel das im schädlichen Raum (S) der zuführenden Atemwege bleibende Volum verloren. Die physiologische Größe von S ist zwar veränderlicher als die anatomische Größe. Es soll für diese schematisierende Betrachtung davon abgesehen werden. S ist für den Erwachsenen bei Nasenatmung ca. 0,16 Liter. Das *nutzbare Volum eines Atemzuges* ist $Q - S$. Das *nutzbare Minutenvolum* N ist gleich dem Minutenvolum $L - n\,S$, also $L = N + n \cdot S$. In die Arbeitsformel eingesetzt, gibt:

$$A = \left(\frac{k_{el}}{2} \cdot \frac{1}{n} + \frac{k_w}{30}\right)(N + n \cdot S)^2 .$$

Wenn N als Konstante betrachtet wird, als die nutzbare Leistung, welche mit verschiedener Frequenz erreicht werden kann, ergibt die Differenzierung $\frac{dA}{dn}$ und Auflösung des gleich Null gesetzten Differentialquotienten die optimale Atemfrequenz n_o, bei welcher die nutzbare Liefermenge mit geringster Atemarbeit geleistet wird.

$$n_o = \sqrt{K^2 + 2K \cdot \frac{N}{S}} - K \quad [4]); \qquad K = 3{,}75 \cdot \frac{k_{el}}{k_w} = 3{,}75 \cdot \frac{14}{4} = 13{,}1 .$$

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[1]) LILJESTRAND: l. c. S. 245.

[2]) Auch der Bau der Atemarbeitsformel entspricht vielleicht noch nicht ganz den tatsächlichen Verhältnissen. Der experimentelle Befund, daß bei willkürlicher maximaler Atemanstrengung die Minutenleistung oberhalb einer optimalen Atemfrequenz wieder sinkt (S. 121), ist nach der Formel nicht zu erwarten, indem die Arbeitsgröße für eine bestimmte Minutenleistung nach der Formel mit der Frequenz dauernd abnimmt. Entweder ist der Phasenwechsel mit Umsteuerungswiderständen (z. B. Massenträgheit) verbunden, welche in der Formel noch nicht berücksichtigt sind und bei höheren Frequenzen zunehmend Bedeutung gewinnen, oder dann ist die Formel richtig und vermindert sich die mechanische Leistungsfähigkeit der arbeitenden Muskeln mit steigender Frequenz.

[3]) ROHRER: Die Regulation der Atmung. Schweiz. med. Wochenschr. 1921, Nr. 4, S. 74—79.

[4]) Die Umformung $n_o = K\left(\sqrt{1 + \frac{2}{K} \cdot \frac{N}{S}} - 1\right)$ weniger geeignet zur Diskutierung.

Bei einem Ruheminutenvolum von 7 Litern und 15 Atemzügen pro Minute ist das nutzbare Atemvolum $N = L - n \cdot S = 4{,}6$ Liter.

Die Berechnung von n_0 für $N = 4{,}6$ Liter gibt $n_0 =$ ca. 17. Es wird also *bei ruhiger Atmung eine Frequenz eingehalten*, welche den erforderlichen *Lungenluftwechsel mit geringster mechanischer Arbeitsleistung erzielt*. Für die Annahme, daß die Ökonomie der Atemarbeitsleistung, die Einstellung auf eine optimale Frequenzzone, für die Regulation der Atemfrequenz maßgebend ist, spricht auch folgendes: Eine Steigerung der Lungenventilation bei Körperarbeit bedingt im allgemeinen eine Frequenzzunahme. Nach vorstehender Formel ist eine Zunahme von N mit einem Wachsen von n_0 verbunden. Bei Frauen und Kindern ist k_a und damit K und n_0 größer als bei Männern mittleren Alters. Die beobachteten Frequenzen liegen tatsächlich ebenfalls höher. Eine Zunahme des Atemwiderstandes k_w oder schädlichen Raumes bedingt nach der Formel ein Sinken der optimalen Frequenz, welches im allgemeinen auch den Beobachtungen entspricht (S. 79). Eine Verminderung des Atemwiderstandes (Mundatmung) führt umgekehrt zu oberflächlicher frequenterer Atmung.

Es ist bei anderen rhythmischen Bewegungsvorgängen von Skelettmuskelgruppen, z. B. bei der Gangbewegung, oder oft ausgeführten rhythmischen Arbeitsbewegungen[1]), eine bekannte Beobachtung, daß die Rhythmik sich den in dem bewegten Körperabschnitt und den äußeren Widerständen gegebenen mechanischen Bedingungen anpaßt. (Gangrhythmik bei verschieden großen Individuen, bei verschiedener Bewegungsschnelligkeit, verschiedener Steigung oder Unebenheit des Untergrundes.) Die Bewegung schleift sich ein auf eine günstige Ausnützung der Muskelarbeit, wobei die propriozeptiven Empfindungen in den bewegten Körperteilen und das Anstrengungsgefühl unbewußt leitend sind. Bei den Atemorganen kommen als solche Einflüsse außer propriozeptiven, sensiblen Reizen in der bewegten Körperstammwandung[2]) und der Lunge (Vagus) auch die durch den Atemluftstrom in den Schleimhäuten der oberen Luftwege bedingten Reize in Frage.

Daß dieses Moment wahrscheinlich auch bei der Regulation der Atemrhythmik wichtig ist, dafür spricht die Erscheinung, daß bei plötzlicher Änderung der atemmechanischen Verhältnisse ein *Übungsstadium* beobachtet wird: z. B. eine Widerstandsvermehrung durch einen Atemapparat (Gasmaske, S. 79) führt zunächst individuell zu wechselnden Frequenzänderungen. Im Laufe der Zeit kommt dagegen bei den meisten Versuchspersonen eine gleichmäßige Einstellung auf eine erniedrigte Frequenzzone zustande. Nach eigenen Untersuchungen zusammen mit HISHIKAWA[3]) über die Atmung des Neugeborenen ist in den ersten Lebenstagen ein solches Übungsstadium deutlich zu beobachten, eine zunächst individuell erheblich wechselnde Frequenzeinstellung. Nach einigen Tagen verringert sich der Schwankungsbereich, um im Laufe des ersten Lebensjahres noch weiter abzunehmen.

Die Einstellung der Atemfrequenz auf eine optimale Frequenzzone wird durch zahlreiche reflektorische und psychische Einflüsse auf die rhythmische Tätigkeit des Atemzentrums immer wieder zeitweise überlagert oder längere Zeit gestört (z. B. willkürliche Änderung der Atemfrequenz bei Phonation, oberflächliche frequente Atmung durch Pleuraschmerzen, neurotische Atemstörungen). Bei Beseitigung solcher Einflüsse zeigt sich immer wieder die Tendenz zur Rückkehr zur optimalen Frequenzzone, ein Zeichen dafür, daß dieses Moment hauptsächlich die Frequenz bestimmt.

Die *chemische Regulation* der Atemleistung und die *Regulation der Atemrhythmik* stehen in einem *Ergänzungsverhältnis*.

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[1]) ATZLER, Berufliche Arbeit als physiolog. Problem. Vers. d. Deutsch. Naturforscher u. Ärzte, Innsbruck 1924. Die Naturwissenschaften, Heft 47, S. 1039. 1924.

[2]) Bedeutung afferenter Bahnen der Intercostalnerven und des Phrenicus für die Atemregulation: LILJESTRAND, Atmung. Jahresberichte über die ges. Physiologie, S. 259. 1922.

[3]) HISHIKAWA: Schweiz. med. Wochenschr. 1923, Nr. 13.

VII. Funktionelle und plastische Anpassung der Atemorgane.

a) Funktionelle Anpassung der Atemorgane.

Der Zustand der Atemorgane und der Ablauf der Atembewegung passen sich wechselnden statischen, dynamischen und energetischen Bedingungen an (S. 105 und 120).

Die Untersuchung des Verhaltens eines bestimmten Individuums oder der Veränderung des normalen Zustandes durch bestimmte Erkrankungen an den Atemorganen erfordert die systematische Feststellung der mechanischen Bedingungen unter verschiedenen Umständen[1]).

Neben der messenden und graphisch registrierenden Beobachtung des Verlaufes der ruhigen und der willkürlich maximal gesteigerten Atmung (von denen die erstere außer den mechanischen Bedingungen auch regulatorische Verhältnisse [chemische und nervöse Atemregulation] widerspiegelt, die letztere im wesentlichen rein die Grenzverhältnisse des mechanischen Vorganges kennenlernt: Bewegungsspielraum, maximaler Atemdruck, maximales Minutenvolumen) wäre besonders für die pathologische Physiologie der Atemorgane auch der Ausbau einer eigentlichen *funktionellen Untersuchungsmethodik* wichtig. Die funktionelle Diagnostik der Leistungsfähigkeit von Organen vergleicht im allgemeinen die Änderung der Organfunktion bei bestimmt dosierten Belastungen der Organtätigkeit. Auf atemmechanischem Gebiet würde es sich um die abgestufte Änderung von Faktoren handeln, welche die Atemarbeit bestimmen, z. B. Feststellung der Anpassung der Atembewegung an dosierte Vergrößerungen des Luftströmungswiderstandes, und des schädlichen Raumes[2]).

b) Plastische Anpassung der Atemorgane.

Die Atembewegung wirkt zurück auf den Zustand der Atemmuskeln und den Bau der statisch und dynamisch beanspruchten Weichteile und Skelettabschnitte. Es ist anzunehmen, daß die *normalen Wachstums- und Umbildungsvorgänge* an *Lunge und Brusthöhlenwandung* von der Atemfunktion beeinflußt sind. Außerdem ist auch die Beanspruchung der Atemmuskeln bei Körperstammbewegungen (S. 91) mitbeteiligt. Beide Momente sind für eine Übungstherapie von Unterentwicklungszuständen der Atemorgane wegleitend.

Die *Pathologie der Atemorgane* zeigt viele Beispiele, wo die Atemfunktion bei der Entstehung von Bauänderungen der Lunge und Brusthöhlenwandung mitwirkt (Emphysem, Asthma), wo ferner plastische Anpassungen im Rahmen der neuen Bauverhältnisse den Ablauf der Atembewegung günstig gestalten. Die funktionelle Atemtherapie besteht in einer bewußten Leitung dieser Anpassungsvorgänge. (S. Abschnitte über Pathologie der Atemfunktion, ferner: HOFBAUER: Atmungspathologie und Therapie. Berlin: Julius Springer 1921.)

VIII. Schluß.

In diesem Abschnitt über die *Physiologie der Atembewegung* ist versucht worden die mechanische Seite des Atemvorganges systematisch aufbauend darzustellen, bis zu einer Grenze, wo dieser Begriffskreis sich mit denjenigen anschließender Gebiete berührt. (Atem*innervation*; *Lungengaswechsel*: Nutzbares Atemvolum, Bedeutung für Regulation der Atemfrequenz.)

Die Darstellung ist an manchen Stellen ein Gerüst, das auf ein wenig umfassendes Versuchsmaterial aufbauen mußte (Statik, Dynamik, Energetik der Atmung), da eine Vergleichung mit Befunden anderer Untersucher oft nicht möglich war. Weitere Untersuchungen werden Ergänzungen, vielleicht auch Änderungen bringen.

Besonders wichtig erschien der Anschluß an den *klinischen atmungspathologischen Gedankenkreis*, für welchen vor allem die *Topographischen Fragestellungen*, (siehe Sachregister: *Topographie*), den physiologischen Unterbau darstellen können. Die Anwendung auf pathologisch-physiologische Fragen bedarf einiger Vorsicht, da die pathologischen Veränderungen von Lungenbau, Pleuraspaltraum, Brusthöhlenform und Wandung, vom normalen Geschehen sehr abweichende Bedingungen schaffen können. (S. 77, S. 94, S. 100, S. 117.)

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[1]) ACHARD u. BINET: Examen fonctionel du poumon. Paris: Masson et Cie. 1922.

[2]) ROHRER: Begutachtung der schweizerischen Gasmaske. Schweiz. med. Wochenschr. 1921, Nr. 41.

Nachtrag 1, zu S. 91.

Tabelle 8. Strömungsgeschwindigkeit in verschiedenen Abschnitten der Luftwege. (Besprechung der Tabelle siehe S. 91 u. 92.)

	Relative Geschwindigkeit	Gewöhnliche Atmung met sec.	Maximale Atmung met sec.	Hustenstoß met sec.
Glottis	3,39	3,0 —5,0	21,0 —35,0	50 —120
Trachea	1	0,9 —1,5	6,2 —10,0	15 — 35
Rechter Stammbronchus	0,9	0,8 —1,3	5,6 — 9,0	13 — 32
Bronch. v. d = 6 mm . .	1,64 —1,76	1,4 —2,6	10,0 —18,0	24 — 62
„ „ d = 2 mm . .	0,28 —1,25	0,25—1,8	1,7 —13,0	4 — 44
Lobularbronchus	0,35 —0,72	0,3 —1,1	2,2 — 7,0	5 — 25
Intral. Bronch. 5. Ordn. .	0,08 —0,166	0,07—0,24	0,5 — 1,7	1,2— 6
Bronch. resp. 3. Ordn. . .	0,035—0,072	0,03—0,11	0,22— 0,74	0,5— 2,5

Nachtrag 2, zu S. 116.

Der Widerstand in den Luftwegen ist, außer durch Schleimhautschwellungen im nasalen und bronchialen Abschnitt, vor allem durch verschiedenen Kontraktionszustand der Ringmuskulatur der intrapulmonären Luftkanäle veränderlich. Die Bronchialmuskulatur scheint hinsichtlich ihrer Innervation nicht in relativ selbständige Bezirke eingeteilt zu sein wie die Arterienmuskulatur. Ihre Aufgabe ist eine Regulation des Gesamtströmungswiderstandes in den Luftwegen, (z. B. Schutzreflex bei Einatmung reizender Gase). Für eine Regulation der Strömungszuteilung auf verschiedene Lungenabschnitte durch regional begrenzte Bronchialverengerungen liegen keine Anhaltspunkte vor. Im Gegensatz zum Gefäßsystem, wo die Verteilungsregulation im Vordergrund steht und pathologisch-physiologisch zahlreiche örtlich begrenzte vasomotorische Neurosen relativ selbständiger Strömungsgebiete vorliegen können, ist bei den Atemorganen nur ein über die ganzen intrapulmonären Luftwege sich erstreckender Spasmus der Bronchialmuskeln beobachtet (Asthma bronchiale). Über halbseitige oder lobär begrenzte Asthmaanfälle fehlen Angaben.

IN: Underwater Physiology. Proceedings of the Fourth Symposium on Underwater Physiology. New York, Academic Press, 1971, p. 347–356.

ARTERIAL BLOOD GASES, HEART RATE, AND GAS EXCHANGE DURING REST AND EXERCISE IN MEN SATURATED AT A SIMULATED SEAWATER DEPTH OF 1000 FEET

J. Salzano, E. M. Overfield, D. C. Rausch, H. A. Saltzman, J. A. Kylstra, J. S. Kelley, and J. K. Summitt

A simulated dive to an equivalent depth of 1000 FSW (31.3 atm abs) in Duke University's hyperbaric chambers—a dive undertaken in collaboration with the U.S. Navy—provided the opportunity to investigate several intriguing questions. Can P_{O_2} and P_{CO_2} in blood be measured at 1000 FSW with currently available laboratory equipment? How does breathing a He–O_2 atmosphere, which is 4.4 times as dense as air is at sea-level pressure, influence gas exchange in normal divers? Does breathing almost pure inert gas alter the difference between the mean partial pressures of oxygen in alveolar gas and arterial blood? Can moderately heavy exercise be performed at 1000 FSW? Finally, how does the physiologic response to exercise differ at this pressure from the response at sea level?

Methods

Physiological measurements were obtained from each of three healthy male volunteers during alternating periods of exercise and rest. Studies were performed on two or more occasions at the surface, once when the subjects were saturated at a simulated seawater depth of 320 ft (10.7 atm abs), and once when they were saturated at a simulated depth of 1000 FSW (31.3 atm abs), within a dry compression chamber.

The atmosphere in the chamber was monitored continuously with equipment, located outside the chamber, that was sensitive to CO_2 concentrations of 1.25 ppm and to O_2 concentrations of 250 ppm. Except for the inspired P_{CO_2}, all analyses were performed inside the compression chamber at ambient pressure.

The data were collected while each subject, seated on a Fleisch bicycle ergometer, breathed ambient gas through a low-resistance respiratory valve having a dead space of 160 ml. The work load of the ergometer was not affected by changes in the density of the gaseous environment.

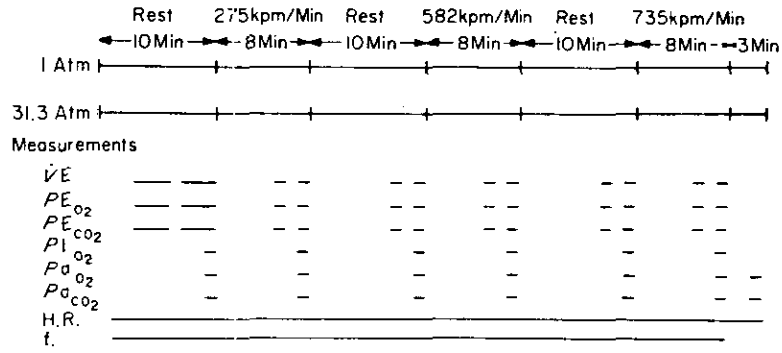

FIG. 1. Diagrammatic representation of experimental sequence used in this study. Continuous lines at the top of the figure indicate that the periods of alternating rest and work were uninterrupted. The time and duration of each measurement are indicated by the position and length of each line in relation to the timing sequence above.

The experimental sequence is shown in Fig. 1. At 31.3 atm abs, the final period of work at 735 kpm/min (kilopond) was extended for 3 min without the respiratory valve to evaluate how the external resistance of the breathing assembly influenced the steady state pressure of CO_2 in arterial blood (Pa_{CO_2}).

Samples of arterial blood, mixed expired gas, and inspired gas were collected simultaneously at specific times, both under conditions of rest and exercise, according to the schedule shown in Fig. 1. Arterial blood was collected anaerobically in iced glass syringes. Expired gas was collected in Douglas bags, and volumes per unit time ($\dot{V}_E$) were measured by use of a modified 120-L Tissot gasometer. Inspired gas was sampled from a site immediately upstream to the respiratory valve. The times of sample collection were the same at depth and at surface so that it could be determined if the interval required to reach a steady state during work and the rate of recovery from work were the same under both conditions. Heart rate (HR) and respiratory frequency (f) were recorded continuously during each experimental sequence on a polygraph positioned outside the chamber.

Measurements of P_{O_2} and P_{CO_2} in the respired gas and arterial blood were made electrochemically with commercially available electrodes. The electrodes and three rotating flask-type tonometers were all contained in the same water bath, which was maintained thermostatically at 37°C (verified with a hydrostatically pressure-calibrated mercury thermometer).

Specially prepared gas mixtures, certified to be accurate within 5 ppm, were used for calibration (42 ppm equals a partial pressure of 1 mmHg at 1000 FSW). The electrodes were calibrated with at least four different gas mixtures. Oxygen tensions in blood measured at depth were corrected by multiplication with the tonometer factor, also determined at depth. Body temperature was measured sublingually with a thermistor probe, which had been previously calibrated in the water bath at 37°C.

Identical studies also were performed at a simulated depth of 320 FSW (10.7 atm abs) while the subjects breathed a gas consisting of 97% He and 3% O_2. At this depth, however, the only valid measurements obtained were those of pulse and respiratory rate.

In addition to the three subjects, a physician and a technician participated in the simulated dives. Each participant was assigned and trained to make specific measurements during the

TABLE I

MEAN VALUES[a] OF PULMONARY VENTILATION ($\dot{V}_E$), O_2 CONSUMPTION ($\dot{V}_{O_2}$) AND CO_2 ELIMINATION ($\dot{V}_{CO_2}$) FOR THREE SUBJECTS AT REST AND DURING EXERCISE AT SEA LEVEL (1 ATM ABS) AND SATURATED AT A SIMULATED DEPTH OF 1000 FSW (31.3 ATM ABS)

Condition (kpm/min)	Pressure (atm abs)	No.	$\dot{V}_E$, (L/min, BTPS) Mean	$\dot{V}_E$, (L/min, BTPS) Range	$\dot{V}_{O_2}$ (ml/min, STPD) Mean	$\dot{V}_{O_2}$ (ml/min, STPD) Range	$\dot{V}_{CO_2}$ (ml/min, STPD) Mean	$\dot{V}_{CO_2}$ (ml/min, STPD) Range
Rest	1	21	11.9	9.1–16.4	336	286–404	300	253–393
	31.3	6	11.0	9.2–13.1	381	293–469	310	227–387
275	1	18	23.7	22.1–26.9	930	774–1036	828	744–967
	31.3	6	25.1	22.0–28.6	1109	1043–1228	928	826–1093
582	1	18	41.7	34.7–47.6	1454	1293–1588	1499	1167–1677
	31.3	4	40.7	38.5–51.1	1791	1654–1950	1664	1535–1791
735	1	16	53.4	47.1–72.1	1799	1552–2101	1870	1666–2107
	31.3	6	51.1	47.0–58.7	2177	1830–2244	1929	1720–2228

[a] *Mean values at rest were calculated from* pooled data of the two measurement intervals of the initial rest period. Mean values during exercise were calculated from pooled data of the two measurement intervals of each work load (Fig. 1). Data were pooled because of their similarity.

surface experiments, and to repeat the same measurements during the dives. The sequence and timing of these rehearsed experiments were supervised continuously by the investigators (who were outside the chamber) through visual and audio contacts with the men inside. Detailed physical examinations of the subjects, prior to and following the dive, including measurements of respiratory function, revealed no abnormalities.

TABLE II

MEAN VALUES[a] OF RESPIRATORY EXCHANGE RATIO AND MEAN ALVEOLAR–ARTERIAL O_2 PRESSURE DIFFERENCE [$(A\text{-}a)\Delta P_{O_2}$] FOR THREE SUBJECTS AT REST AND DURING EXERCISE AT SEA LEVEL (1 ATM ABS) AND SATURATED AT A SIMULATED DEPTH OF 1000 FSW (31.3 ATM ABS)

Condition (kpm/min)	Pressure (atm abs)	Respiratory exchange ratio No.	Respiratory exchange ratio Mean	Respiratory exchange ratio Range	$(A\text{-}a)\Delta P_{O_2}$ (mmHg), No.	$(A\text{-}a)\Delta P_{O_2}$ (mmHg), Mean	$(A\text{-}a)\Delta P_{O_2}$ (mmHg), Range
Rest	1	21	0.88	0.80–0.98	9	16	4–21
	31.3	6	0.81	0.78–0.89	5	31	26–37
275	1	18	0.88	0.76–1.00	4	19	10–28
	31.3	6	0.83	0.79–1.00	3	11	3–24
582	1	18	1.03	0.81–1.20	3	20	17–24
	31.3	6	0.89	0.80–1.00	2	24	23–25
735	1	16	1.04	0.87–1.16	3	19	13–28
	31.3	6	0.96	0.90–1.05	3	25	12–35

[a] *Mean values were calculated as explained in* footnote to Table I.

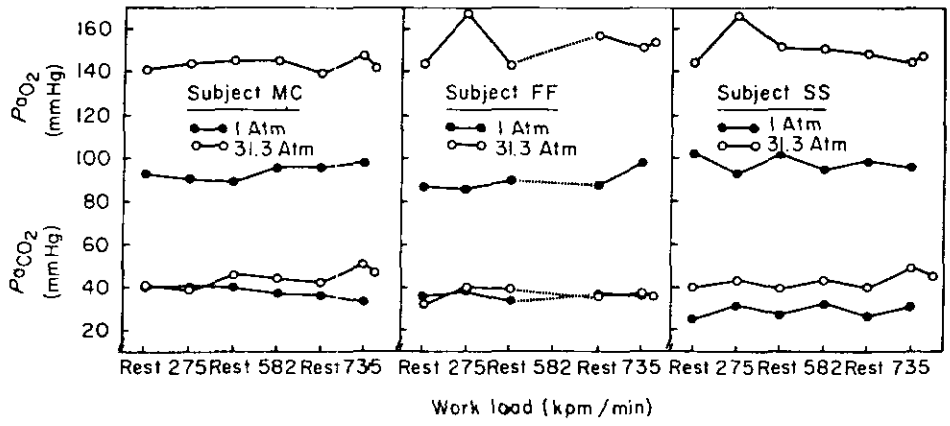

FIG. 2. Arterial P_{CO_2} and P_{O_2} values during rest and work at normal and elevated ambient pressure. Each point represents a single value. The broken line indicates that the second work load value for subject FF at 31.3 atm abs is missing. In subject MC, the Pa_{CO_2} rose from a resting level of 41 mmHg to a maximal value of 51 mmHg at a work load of 735 kpm/min at 31.3 atm abs, but decreased to 47 mmHg while he continued the exercise but no longer breathed through the respiratory assembly. For subject SS, under similar conditions, the values for Pa_{CO_2} were 40, 49, and 45 mmHg, respectively. The Pa_{CO_2} did not increase significantly from a resting value of 32 mmHg under similar conditions in subject FF.

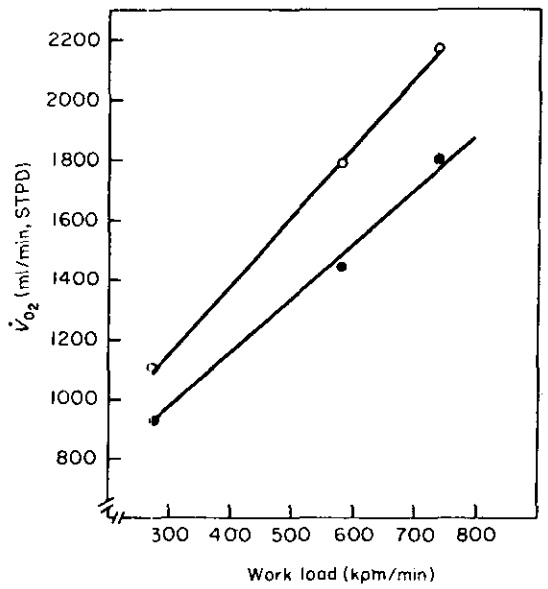

FIG. 3. Oxygen consumption ($\dot{V}_{O_2}$) at various work loads at sea level and elevated ambient pressure. Each point is the mean value from three subjects. Means were calculated as explained in footnote to Table I. (●) 1 atm; (○) 31.3 atm.

TABLE III

MEAN VALUES[a] OF RESPIRATORY RATE AND HEART RATE FOR THREE SUBJECTS AT REST AND DURING EXERCISE AT SEA LEVEL (1 ATM ABS), AND SATURATED AT SIMULATED DEPTHS OF 320 FSW (10.7 ATM ABS) AND 1000 FSW (31.3 ATM ABS)

Condition (kpm/min)	Pressure (atm abs)	No.	Respiratory rate (breaths/min)		Heart rate (beats/min)	
			Mean	Range	Mean	Range
Rest	1	21	14.4	12.0–17.5	90	78–101
	10.7	6	15.0	13.0–16.3	85	67–94
	31.3	6	12.3	10.0–14.0	79	69–89
275	1	18	18.7	16.0–21.0	108	98–118
	10.7	6	15.9	13.0–21.3	97	80–104
	31.3	6	15.3	13.5–17.0	94	87–97
582	1	18	24.4	15.5–30	138	124–162
	10.7	6	20.6	15.0–26.5	123	106–138
	31.3	6	17.8	15.0–20.0	122	116–129
735	1	16	27.3	22.0–30.0	158	136–172
	10.7	6	20.9	15.0–25.0	139	129–152
	31.3	6	22.9	17.0–30.0	144	126–160

[a] Mean values were calculated as explained in footnote to Table I.

Results

At 31.3 atm abs the inspired O_2 pressure ranged from 216 to 221 mmHg, and the inspired P_{CO_2} was never more than 0.5 mmHg (21 ppm). There did not appear to be any consistent difference between pulmonary-gas-exchange values obtained during rest at surface pressure and those obtained at depth, except for the higher arterial P_{O_2} and larger alveolar–arterial P_{O_2} differences [(A–a) ΔP_{O_2}] (Tables I, II; Fig. 2). (In one subject at 14.6 atm abs, the inspired O_2 tension was virtually identical to what it had been at the surface when he breathed air, but the mean difference in alveolar–arterial O_2 tension was still greater than it was at surface pressure.)

In general, the patterns of responses to work at 31.3 atm abs resembled those of healthy individuals working at 1 atm abs pressure. In comparison with work performed at sea-level pressure, each work load at depth was performed with a greater $\dot{V}_{O_2}$ (Fig. 3; Table I), unchanged or greater $\dot{V}_{CO_2}$ (Table I), lower heart rate (Table III; Fig. 4), lower respiratory rate (Table III), larger tidal volume, lower ventilatory equivalent for O_2 ($\dot{V}_E/\dot{V}_{O_2}$) (Fig. 5), and greater O_2 pulse ($\dot{V}_{O_2}$/heart beat) (Fig. 4). Moderate arterial hypercapnia occurred in two subjects during exercise at depth (Fig. 2).

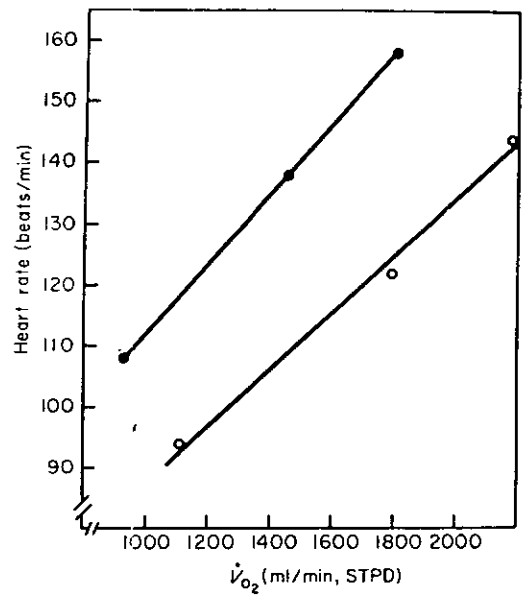

FIG. 4. Relationship of heart rate to O_2 consumption ($\dot{V}_{O_2}$) at normal and elevated ambient pressure. Each point is the mean value from three subjects. Means were calculated as explained in footnote to Table I. Oxygen pulse can be computed from the $\dot{V}_{O_2}$/heart rate ratio. (●) 1 atm; (○) 31.3 atm.

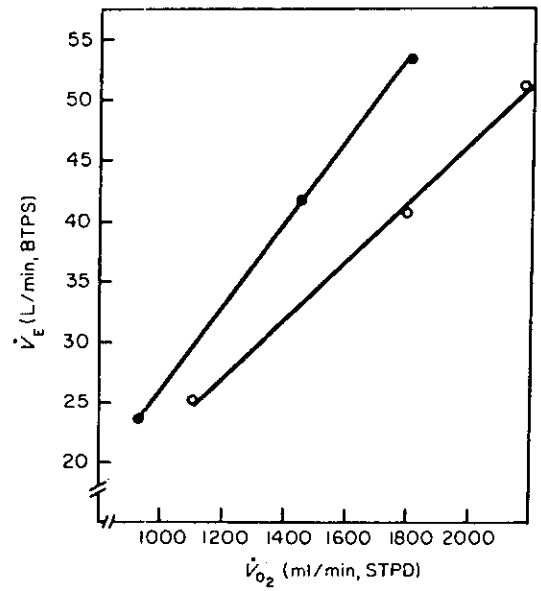

FIG. 5. Relationship of pulmonary ventilation ($\dot{V}_E$) to O_2 consumption ($\dot{V}_{O_2}$) at sea level and elevated ambient pressure. Each point is the mean value from three subjects. Means were calculated as explained in footnote to Table I. The O_2 ventilatory equivalent can be computed from the $\dot{V}_E/\dot{V}_{O_2}$ ratio. (●) 1 atm; (○) 31.3 atm.

Discussion

Respiratory gas exchange at 1000 FSW while the subjects were at rest appeared in general to be normal except for a larger (A–a) ΔP_{O_2} difference. These findings confirm those of Hamilton (10) who studied minute ventilation, O_2 consumption, and end-tidal P_{CO_2} in men at 660 FSW.

If ventilation and perfusion are not uniformly balanced, as is the case when humans stand erect (26), then breathing a gas mixture with a greater than normal inert gas fraction should result in an increased (A–a) ΔP_{O_2}. The results of experiments by Lenfant (15) and Cole and Bishop (4, 5) have provided evidence that the lungs of normal men contain a small number of alveoli with extremely low ventilation–perfusion ratios. Thus a larger than normal inert gas fraction in the inspired gas might well result in an increased (A–a) ΔP_{O_2} in normal men (21). When 99.1% inert gas was breathed at 1000 FSW, the (A–a) ΔP_{O_2} was indeed greater than at surface pressure during air breathing. However, a variety of other factors may be involved: (*1*) an increased PI_{O_2} could increase the (A–a) ΔP_{O_2} as a result of any true shunts; (*2*) increased gas density could impair diffusion in the airway; and (*3*) increased gas density might cause a redistribution of ventilation. To test these possibilities, we repeated the studies at 450 FSW, using one subject who breathed 98.6% inert gas with a density 2.08 times greater than air at sea level pressure. The PI_{O_2} was 148.5–150 mmHg, yet the (A–a) ΔP_{O_2} was still greater than it was at sea level. The second and third possibilities above cannot be ruled out, but it seems likely that the increased (A–a) ΔP_{O_2} was due at least in part to the greater inert gas fraction of the respired medium.

The increased $\dot{V}_{O_2}$ for a given ergometric load at 31.3 atm abs (Fig. 3) can be attributed in large part, or entirely, to the increased work of breathing the denser gas (1, 17, 18). To provide a convenient, valid estimate of the O_2 cost of ventilation during moderate exercise at sea level pressure while air is breathed, a value of 2 ml O_2/L $\dot{V}_E$ has been selected (3, 16, 19, 20). If the observed $\dot{V}_{O_2}$ increase at depth was due entirely to the greater effort necessary to ventilate a gas that is 4.4 times as dense as air at surface pressure, then the cost of breathing during exercise at 31.3 atm abs for two of the three subjects can be calculated to have been 8 to 10 ml O_2/L $\dot{V}_E$. This estimated four- to fivefold increase in O_2 cost of breathing is similar to that observed by Glauser *et al.* (7) when normal subjects were induced to hyperventilate with a 7% CO_2–73% SF_6–20% O_2 mixture. An 80% SF_6–20% O_2 mixture at 1 atm has a density equivalent to that of an He–O_2 mixture containing one-fifth of an atm of O_2 at 30 atm. Although each work load required a greater O_2 uptake at 31.3 atm abs (Fig. 3), there was no convincing evidence that work performance was limited by the O_2 cost of breathing.

The reduction of heart rate observed in this study at 10.7 atm abs indicates that the extent of bradycardia does not correlate in a linear manner with increases either in hydrostatic pressure or in the inspired pressure of He (Table III). At the same time, the occurrence of bradycardia at 10.7 atm abs when the gas density is similar to that of air at sea level, and when there is no marked increase in PI_{O_2}, rules out significant negative chronotropic contributions by these factors at greater depths unless other interactions take place.

Previous reports have indicated that bradycardia occurs when man is exposed to a hyperbaric environment. Hamilton (10) found that the heart rates of two subjects exercising at 620 FSW in a He–O_2 environment were slower than they were at an equivalent $\dot{V}_{O_2}$ at the surface. Hesser *et al.* (11) showed that elevated PI_{O_2} was only partially responsible for rela-

tive bradycardia during exercise while subjects breathed air at 4.5 atm abs. They found that increased N_2 pressure and gas density were partially responsible as well. Other reports (6, 23, 27) document the occurrence of bradycardia in man breathing O_2 at pressures of 1 atm abs or greater. In our study, the PI_{O_2} was below the level that would cause the observed bradycardia. Another possible explanation for this condition in a hyperbaric He environment is a cardiovascular response to peripheral vasoconstriction that must accompany the known decrease in skin temperature in the He environment (22). From the available evidence, a valid single explanation for bradycardia at depth is lacking.

The net result of the increased O_2 pulse (that is, the volume of O_2 transported per heart beat) at depth is that O_2 transport to tissues is maintained despite a decrease in heart rate (Fig. 4). Hesser *et al.* found that O_2 pulse increased with a rise in PI_{O_2} to 1 atm abs, and that it increased still further with a rise in P_{N_2} during exercise with air at 4.5 atm abs. Thus, the evidence from previous and present studies is that the increase of O_2 pulse at depth may be a response to the same causative factors involved in bradycardia.

Slower respiratory rates at depth (Table III) may represent a mechanism whereby the work required to overcome the increased nonelastic resistance to breathing the denser gas is less than it would be if the respiratory rates observed at the surface had been maintained. Hesser *et al.* have recently reported similar findings in subjects exercising at 4.5 atm abs while breathing air. They showed that the slower respiratory rates and larger tidal volumes under these conditions were related to the density of the respired gas.

In the present study, minute ventilation ($\dot{V}_E$) in response to a given ergometric load was similar at the surface and at depth (Table I), but was less for a given $\dot{V}_{O_2}$ at depth (Fig. 5). This reduction in the ventilatory equivalent for O_2 ($\dot{V}_E/\dot{V}_{O_2}$) implies a greater efficiency of O_2 transfer from the atmosphere to the blood if all other conditions of gas exchange remain constant. In our study, however, the conditions were dissimilar in that the PI_{O_2} at the simulated depth of 1000 FSW was higher, $\dot{V}_{O_2}$ was greater, and significant arterial hypercapnia occurred in two subjects during performance of the heaviest work load.

Reductions in the ventilatory equivalent for O_2 have been reported under a variety of conditions in which the common factor was increased breathing resistance because of airway obstruction or increased gas density that led to a lower level of ventilation (8, 9, 11, 25).

That relative alveolar hypoventilation did occur during exercise at depth in this study is indicated by the occurrence of hypercapnia in two subjects who exercised at the highest work load (Fig. 2), but whose Pa_{CO_2} in the intervening rest periods returned to or toward baseline values. These findings cannot be explained by an elevated PI_{CO_2}, for its valves did not exceed 0.5 mmHg at 31.3 atm abs.

Alveolar hypoventilation with concomitant elevations in Pa_{CO_2} has been reported during exercise in hyperbaric conditions (10–14). This response has been shown to be related in part to an increased PI_{O_2} and in part to the increased resistance of breathing a denser gas. In the present investigation, however, the increase in PI_{O_2} was comparatively small and should not have influenced ventilation significantly (Table III).

It has been suggested that alveolar hypoventilation in response to an increase in airway resistance is an adaptive reaction in man—i.e., hypercapnia is better tolerated than the increased work of breathing required to maintain normal CO_2 levels (2). This response has been shown to be especially characteristic of divers (13, 14, 24). It is of interest that the two subjects (MC and SS) who manifested hypercapnia during exercise at depth were (and are

currently) active divers, whereas the third subject, who maintained normal CO_2 levels, had not worked as a diver in recent years.

Breathing resistance in the present study was elevated by the increased density of the gas and the inherent resistance of the breathing assembly. At least part of the hypercapnia during exercise in subjects MC and SS can be attributed to the resistance of the breathing valve, since Pa_{CO_2} fell in both subjects when they exercised at a 735 kpm/min work load without breathing through the respiratory assembly (Fig. 2). It is possible that any substantial increase in external breathing resistance may exceed the adaptive capabilities of man working at a relative density of 4.4. That this limitation may be serious is apparent when one compares the much greater resistance of underwater breathing valves with the low resistance of the breathing assembly used in the present physiological studies.

The conclusions from this study are that work at a pressure equivalent to 1000 FSW is not detectably limited. Gas exchange in divers breathing 99.1% He and 0.9% O_2 during rest at 31.3 atm abs is essentially normal. The slight increase in (A–a) ΔP_{O_2} at 1000 FSW, which was probably caused in part by the high fraction of inspired inert gas, is not of practical significance in normal divers. Normal men can perform moderately heavy exercise, for brief periods at least, at increased environmental pressures simulating those found at depths in the sea of up to 1000 ft. The anticipated relationships among the uptake of O_2 by the body, ergometric work, pulse, and ventilation prevailed at depth. The rate of recovery from exercise was similar to that at surface pressure. Impairment of the capacity to perform work could not be discerned by the physiological methods used, and there was no evidence indicating that the physiological limits of performance had been attained.

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Last, but certainly not least, we thank the five men inside the chamber.

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ABSTRACT

Schaefer, K.E., C.R. Carey and J.H. Dougherty, Jr.

Pulmonary Function and Respiratory Gas Exchange During Saturation-Excursion Diving to Pressures Equivalent to 1000 Feet of Sea Water.

In: Lambertsen, C.J., ed. Underwater Physiology. Proceedings of the Fourth Symposium on Underwater Physiology, p. 357-370. New York, Academic Press, 1971.

The reduction of maximal expiratory flow rate and maximal inspiratory flow rate produced by the rapid compression of four subjects to depths of 600 and 800 FSW at a rate of 2-3.5 ft/min was found to be associated with decreased vital capacity. During the 35- to 36-hr saturation periods at depth the maximum expiratory flow rate rose 44%; maximum inspiratory flow rate and vital capacity increased 23% and 6% respectively. Airway collapse during rapid compression and airway reopening during the subsequent saturation period are suggested as the most likely explanation of the observed changes. However, it is conceivable that phasic changes in vagal stimulation resulting in bronchoconstriction during compression and recovery of a more normal bronchial tone during the saturation period could have caused the observed decrease and subsequent increase in vital capacity and respiratory flow rates. In rest and exercise, $PACO_2$ did not change significantly at depth, but showed considerable individual variations. Pulmonary gas exchange at rest remained within normal limits at depths of 800 and 1000 FSW. Exercise performed by two subjects at a moderate work load (100 W) at 800 and 1000 FSW resulted in an increase of O_2 consumption whereas CO_2 excretion tended to decrease. Tidal volume increased and respiratory rate decreased with increasing pressure in rest and exercise. A pronounced bradycardia was observed under both conditions, which we attributed primarily to the effect of inert gas pressure rather than to the effects of elevated PO_2. Urinary CO_2 excretion was significantly elevated during the saturation-excursion and decompression periods. The two subjects who complained about muscle pains in the leg, which did not respond immediately to recompression showed peak urinary CO_2 excretion either at the time the symptoms occurred or during the following days. (Authors' summary)

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Dyspnea in divers at 49.5 ATA: mechanical, not chemical in origin

W. H. SPAUR, L. W. RAYMOND, M. M. KNOTT, J. C. CROTHERS, W. R. BRAITHWAITE, E. D. THALMANN, and D. F. UDDIN

The Navy Experimental Diving Unit, Panama City, FL 32401, and the Naval Medical Research Institute and Department of Medicine, National Naval Medical Center, Bethesda, MD 20014

Spaur, W. H., L. W. Raymond, M. M. Knott, J. C. Crothers, W. R. Braithwaite, E. D. Thalmann, and D. F. Uddin. 1977. Dyspnea in divers at 49.5 ATA: mechanical, not chemical in origin. Undersea Biomed. Res. 4(2): 183–198.—Pulmonary function was studied in six divers living in a hyperbaric chamber at a pressure nearly fifty times normal (49.5 atmospheres absolute (ATA), equivalent to 488 m or 1600 ft seawater (fsw)). As expected, ventilatory function was reduced. At 49.5 ATA, maximum voluntary ventilation (MVV) was 45% less than the control value. Instantaneous rates of gas flow during forced expiration were similarly reduced, especially those flow rates measured high in the lung volume. These reductions occurred despite an apparent increase in functional residual capacity (FRC) and the use of transpulmonary pressures considerably greater than those exerted during the same maneuvers at normal (sea-level) pressure. During underwater work at 49.5 ATA, the divers rapidly became exhausted at moderate levels of oxygen consumption (1.9 liters/min), showing severe dyspnea and impending syncope. These symptoms were not due to retention of carbon dioxide, nor to hemodynamic or metabolic causes. Thus, dense gas breathing, like asthma, exemplifies a state in which severe dyspnea may occur with normal or low arterial carbon dioxide and normal oxygen transport. The physiological adjustments the divers employed were similar to those seen in acute asthma, imposing an elastic load in addition to the flow-resistive work of breathing a gas mixture eight times as dense as air. Although men can do moderate work under conditions similar to those of this experiment, they will have only a limited physiological reserve available to meet the possibilities of emergencies or respiratory infections.

asthma
carbon dioxide
exercise
helium

Technical advances in the past four decades have made it possible to study man's performance at pressures more than 60 times normal (equivalent to 2000 ft seawater (fsw)) using helium–oxygen breathing mixtures. Such studies are generally done in hyperbaric chambers ashore, but open-sea dives deeper than 1100 fsw have recently been made. This sort of diving has commercial, scientific, and military uses, but the safe depth limits for human exposure are not yet known, nor are the factors which may set such limits. One limiting factor may be the ability of the respiratory system to support metabolic processes at great depths. Even with helium–oxygen breathing mixtures, gas density exceeds a value seven times normal (air, 1 ATA) at 1600 fsw.

We have considered the question of respiratory function at great depths, and this study reports the results of measurements made in a hyperbaric chamber complex at a maximum pressure near 50 ATA. This pressure was selected because we wished to study man's ability to work underwater, and therefore needed to avoid the more serious neurological disturbances which occur at greater pressures (Hunter and Bennett 1974).

MATERIALS AND METHODS

Six males were selected from healthy U.S. Navy divers who volunteered for the experiment. Two were hospital corpsmen, two were physicians, and two were equipment specialists. Their mean age was 31 yr, height 183 cm, weight 85.3 kg, and vital capacity 5.4 liters, BTPS. Five of the six were nonsmokers. After a period of training and base-line examinations, the divers were gradually subjected to increasing pressure by the addition of helium to a hyperbaric chamber complex in which they lived for 32 days. Chamber P_{O_2} was continuously monitored by a conventional fuel cell, and was maintained at 0.30 to 0.35 ATA by continuous addition of oxygen. The first week of the dive was spent in gradual compression to 49.5 ATA. During the second week, the divers performed experiments, including work on a bicycle ergometer in an adjoining chamber while immersed in 35°C water. During immersion, a mixture of helium and oxygen (49 ATA helium, 0.3–0.5 ATA O_2) was supplied from a U.S. Navy Mark 10 closed-circuit underwater breathing apparatus (Majendie and Lady 1970). Inspired gas was not humidified directly, but was probably close to being saturated with water vapor because of the recirculating nature of the Mark 10, and because of the chemical reaction of expired carbon dioxide with the absorbent, releasing water vapor. Inspired gas temperature was not measured, but it was probably close to 35°C since the entire Mark 10 apparatus (including breathing hoses) was immersed in water at that temperature.

The general design of the experiments has been described earlier (Spaur 1974; Raymond, Thalmann, Lindgren, Langworthy, Spaur, Crothers, Braithwaite, and Berghage 1975). This study presents the measurements of pulmonary function in the divers at 49.5 ATA. Three kinds of measurements were made. First, lung volumes and gas flow rates, the flow-volume relationship ($\dot{V}$/Vol), and maximum voluntary ventilation (MVV), were measured in the usual way with a wedge spirometer (Med-Science Electronics, St. Louis) and Model 1000 direct-writing X-Y and 2-channel-time recorders (Hewlett Packard Co., Mountain View, CA.). All recorders were located outside the hyperbaric chambers, and outputs from transducers were hard-wired through bulkhead fittings. Second, quasi-static measurements of the pulmonary pressure-volume relationship were made, to define the mechanical behavior of the lungs in this unusual environment (Milic-Emili, Mead, Turner, and Glauser 1964; Raymond and Severinghaus 1971). Transpulmonary pressure was also recorded during $\dot{V}$/Vol and MVV maneuvers and at rest. This group of measurements was made while the divers were unencumbered by immersion and its attendant need for breathing apparatus.

A third set of measurements dealt with gas exchange during immersed exercise at 49.5 ATA. Prior to immersion, the diver underwent cannulation of a radial artery under local lidocaine anesthesia. He then had electrocardiograph leads placed, donned the Mark 10 underwater breathing apparatus, and climbed down a ladder (Fig. 1) into a fiberglass tank which had been installed in a lower chamber of the hyperbaric complex. Completely immersed, the diver mounted a bicycle ergometer and extended his cannulated wrist through a sleeve which penetrated the wall of the tank. A protective surgical glove was removed. A physician stationed outside in the dry area adjacent to the tank connected the radial artery cannula to a pressure transducer, from which heart rate and blood pressure (and pulsus paradoxus) could

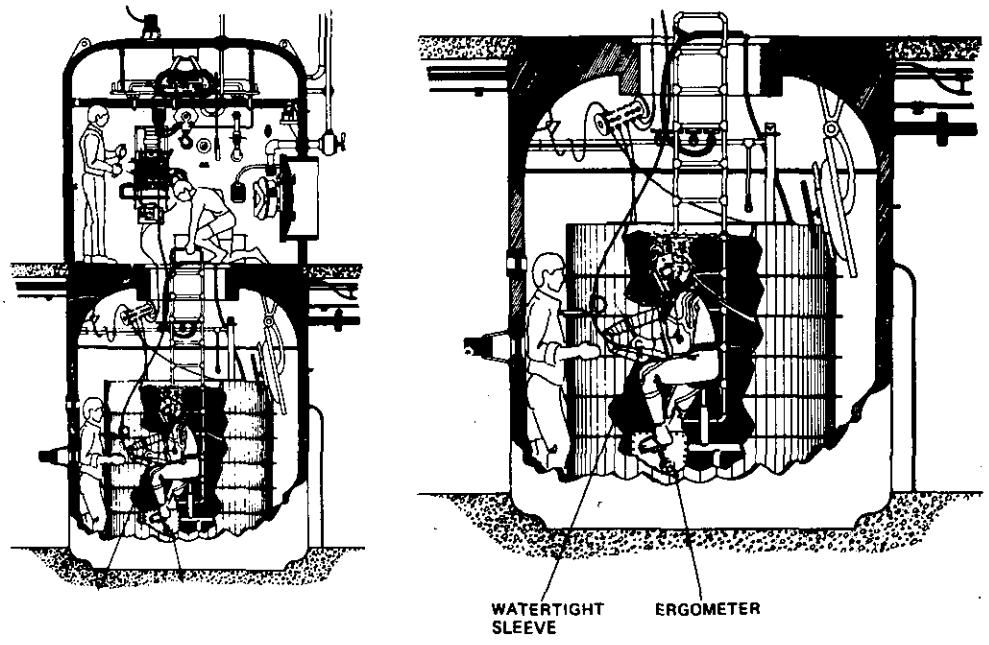

Fig. 1. Overall view (left) and detail (right) of hyperbaric chamber complex, showing upper chamber (igloo) and lower chamber (wet pot).

be continuously recorded. Heart rate was also recorded from the ECG electrodes. Respiratory rate was recorded from a thermistor in the diver's oral-nasal mask and from fluctuations in blood pressure with breathing. Pressure in the oral-nasal mask was also recorded.

Arterial blood samples were taken in heparinized glass syringes during rest, exercise, and recovery at 49.5 ATA. During decompression, arterial blood was also obtained from all six divers during supine rest while they breathed the chamber atmosphere without artificial breathing devices. For the supine conditions, alveolar P_{O_2} was estimated by assuming a respiratory quotient (R) of 0.83, and subtracting the value of arterial P_{CO_2}/R from the inspired P_{O_2} in the manner usually employed when collections of expired gas or end-tidal samples are not available. The use of R = 0.83 for resting divers in the postabsorptive state is supported by observations from the experiment of Raymond and his co-workers (1975) and from earlier ones (Raymond, Bell, Bondi, and Lindberg 1968) at lesser pressures.

Electrodes for the determination of arterial blood P_{O_2}, P_{CO_2} and pH were set up in the upper chamber, using methods developed at the F. G. Hall Laboratory (Duke University Medical Center, Durham, N.C.) and calibrated by the methods of Overfield, Saltzman, Kylstra and Salzano (1969). Methods for sample preparation and analysis for plasma lactate and pyruvate concentrations were adapted from those of Hoborst (1965).

Characteristics of the submersible ergometer

The relationship between oxygen consumption and work rate with the submerged bicycle ergometer requires clarification. The settings of the device (Warren E. Collins, Inc., Braintree, MA) are accurate for nonimmersion work, but the submerged user does additional work against the surrounding water, against his diving suit, and against suit buoyancy under some

conditions. These factors cause $\dot{V}_{O_2}$ for the nonpedaling condition (rest) to be considerably higher than expected for a resting subject. They also cause $\dot{V}_{O_2}$ to be a nonlinear function of the ergometer setting during immersed work. This relationship has been clarified by unpublished measurements made in our laboratory (Table 1). Immersion increased $\dot{V}_{O_2}$ by about 38% in 4 air-breathing subjects at 1 ATA. For comparison, the results of $\dot{V}_{O_2}$ measurements during ergometer work at 49.5 ATA are also shown in Table 1. In these unpublished measurements, $\dot{V}_{O_2}$ was obtained by collection and analysis of mixed-expired gas by the usual methods. For the 49.5 ATA measurements, in which expired-gas collections were not available, $\dot{V}_{O_2}$ was obtained in another manner. While the divers wore the Mark 10 breathing device, their inspired P_{O_2} was kept constant by a matrix of oxygen sensors which sampled the gas stream every 2 s, and activated an oxygen-addition solenoid if any sensor was exposed to a P_{O_2} of less than 0.4 ATA. Since solenoid activity was recorded by an event marker on a strip-chart recorder, the steady-state firing rate of the solenoid provided a measure of $\dot{V}_{O_2}$ because all leaks had been corrected as part of the predive checkout. The solenoid was therefore physically calibrated at 49.5 ATA by displacement techniques, by collecting its oxygen output at representative firing rates in a carefully degreased 13-liter Tissot spirometer and by timing the rate of bell excursion. A calibration of $\dot{V}_{O_2}$ vs. firing rate was constructed after conversion of volumes to STPD conditions.

Characteristics of the underwater breathing apparatus

The breathing equipment used during immersed work in this study was the U.S. Navy Mark 10 Mod 4 mixed-gas apparatus. The basic Mark 10 design has been described by Majendie and Lady (1970). However, its use in an earlier dive similar to that of this study (but with a maximum depth of 1000 fsw) was attended by an unacceptable level of carbon dioxide retention and acidosis at heavy work rates. The Mark 10 was therefore modified to minimize the

TABLE 1

Oxygen consumption during bicycle ergometer work at various ergometer settings and test conditions

Test conditions				Oxygen consumption, liter/min, STPD					
				Ergometer setting, kgm • min^{-1}					
Position	Pressure	Gas	Breathing apparatus	0	150	300	450	600	750
Dry	1 ATA	Air	None	0.35	0.55	0.97	1.22	1.44	1.82
Immersed, head out	1 ATA	Air	None	0.58	–	1.31	1.66	2.09	2.44
Immersed, head out	1 ATA	Air	Mark 10	0.46	0.95	1.41	1.88	2.50	3.14
Immersed fully	49.5 ATA	$He-O_2$	Mark 10	0.62	1.80	1.92	–	–	–

Values are means; $n = 4$ at 1 ATA, $n = 3$ at 49.5 ATA. SEM ranged from 0.04–0.18.

breathing resistance, in particular by using larger breathing hoses and by streamlining elbows and other abrupt geometric transitions in the hoses. The design changes and associated changes in breathing characteristics of the Mark 10 Mod 4 device are described in detail by Cetta and Radecki (1975). Of special interest are the results of measurements of pressure changes in the M-10 oral-nasal mask of the modified Mark 10 when tested with a breathing machine at 49.5 ATA, which simulated human use at that pressure. In this test, the breathing machine manikin generated a tidal volume of 2.0 liters at a breathing rate of 20 breaths per min using a gas mixture of helium with 0.4 ATA oxygen. During inspiration, the oral-nasal mask pressure was 12 cmH_2O below ambient at its minimum and during expiration it was 23 cmH_2O above ambient at its maximum. As the **Results** section below will show, the fluctuations in pressure within the oral-nasal mask during actual use by the divers in the 1600-fsw chamber dive reported in this study were considerably less than the values described by Cetta and Radecki (1975).

RESULTS

Experimental findings will be presented in two main sections: those related to exercise during immersion, and those from ventilatory maneuvers done in the dry, resting state without the encumbrances of breathing apparatus, diving suit, immersion, and arterial cannulation.

Exercise during immersion

The ability of the divers to work was greatly impaired at 49.5 ATA. Of the three men in whom arterial cannulation was successfully accomplished, all were able to complete 6 min of work on the submerged ergometer at the work rate setting of 150 kgm • min^{-1} (Fig. 2, 150 kgm • min^{-1}). Only one man was able to complete the scheduled 6 min of work at the higher ergometer setting (300 kgm • min^{-1}, $\dot{V}_{O_2}$ = 1.92 liter/min). The other two divers stopped work early, due to severe breathlessness and a sense of incipient syncope. The same symptoms occurred in the diver who completed 6 min of 300-kgm • min^{-1} ergometer work, leaving him unwilling to attempt work at the 450-kgm • min^{-1} setting. In contrast, the divers who used this apparatus at lesser pressures (1–10 ATA) prior to the 49.5 ATA studies routinely completed successive 6-min work periods at loads up to 750 kgm • min^{-1} or higher, producing arterial lactate levels of 80–100 mg/dl. In the 1–10 ATA work, the men experienced only mild dyspnea and no presyncopal symptoms.

The divers characterized the sense of breathlessness which limited exercise at 49.5 ATA as an intense drive to inspire. The sensation was mild at the start of work, but became more intense with time at a given work rate. Near exhaustion, it increased with inspiration but persisted into the expiratory phase, as if the full breath had not satisfied some stimulus. Some divers found the symptom alarming in intensity, but noted that it disappeared within 30 s of the end of work, reaching a peak during the 10 s after stopping exercise. Arterial blood gas values at the time of exhaustion (Fig. 2) showed that CO_2 retention was not the limiting factor. Hypoxemia was also excluded, since direct measurements showed that arterial P_{O_2} exceeded 180 mmHg in all samples. Cellular hypoxia was not absolutely eliminated as the cause of breathlessness, but seems unlikely for two reasons: arterial pH remained normal, and plasma lactate levels increased only mildly with exercise, falling to the pre-exercise range within the 6-min recovery period. Heart rate and blood pressure responded normally to exercise (Table 2), minimizing the possibility of hemodynamic abnormalities being the work-limiting factors.

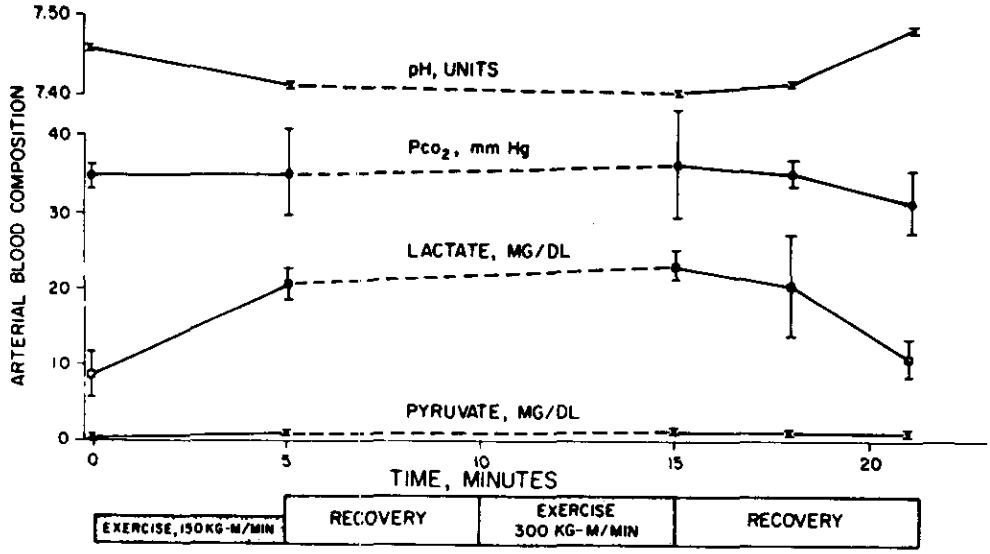

Fig. 2. Responses to underwater work at 49.5 ATA. Severe breathlessness and incipient syncope limited exercise to a maximum ergometer setting of 300 kgm • min^{-1} (see Tables 1 and 2 for other results). Mean values (± SE) are given for divers 2, 5, and 6.

TABLE 2

Cardiorespiratory responses to exercise at 49.5 ATA

Measurement	Rest	Exercise rate, kgm • min^{-1} 150	300	Recovery time, min 3	6
Oxygen consumption, liter/min, STPD	0.62	1.80	1.92	0.80	0.68
Heart rate, min^{-1}	87±7	130±4	137±7	99±7	96±6
Blood pressure, mmHg	126/82	150/85	134/79	132/80	128/83
Respiratory rate, min^{-1}	13±2	21±1	29±1	20±2	18±4
Pulsus paradoxus, mmHg	24±6	27±1	32±7	24±5	23±6
Pressure fluctuations in oral-nasal mask, cmH_2O					
Inspiration	−2.2±0.1	−5.4±0.6	−5.2±0.6	−3.0±0.1	−2.3±0.1
Expiration	4.5±0.2	10.9±1.3	10.5±1.3	6.0±0.2	4.7±0.2

Values are means ± SE; $n = 3$.

However, the blood pressure recordings showed that an abnormal degree of pulsus paradoxus (greater than 10 mmHg) was present during both rest and exercise, suggesting that substantial obstruction to gas flow was present in the divers' airways, or in the breathing apparatus (Rebuck and Pengelly 1973). The rather small fluctuations in oral-nasal mask pressure (Table 2) appear to exonerate the breathing apparatus as the source of the obstruction. It should be pointed out in this regard that breathlessness was reported during even mild exertion during this experiment in the dry, unencumbered state at depths beyond about 1200 fsw. This was noted by all 6 divers, and at 1600 fsw, this sensation often limited conversation to phrases of 5-6 words between breaths.

Spirometry and blood gas composition under dry, resting conditions

More direct evidence of obstruction in the tracheobronchial tree is available from the $\dot{V}$/Vol and MVV measurements. Peak expiratory flow was reduced by almost one-half at 49.5 ATA (Table 3). Flow rates were reduced at all lung volumes as ambient pressure was raised (Fig. 3), despite driving pressures which were much greater than the control values (Table 3). For example, peak expiratory pressures during $\dot{V}$/Vol maneuvers at 49.5 ATA ranged between +140 and +265 cmH_2O, and peak inspiratory pressures ranged between −80 and −96 cmH_2O.

TABLE 3

Effect of living at 49.5 ATA on lung volumes and flow rates and transpulmonary pressures required to generate maximal flow rates during maximum voluntary ventilation (MVV) and forced expiratory flow-volume maneuvers.

Pulmonary function measurement	Atmosphere breathed and total pressure		
	Air, 1 ATA	$He-O_2$, 49.5 ATA	$He-O_2$, 1.2 ATA
Lung volumes			
Vital capacity, liters	6.0–6.2	5.9–6.0	6.1–6.2
Expiratory reserve volume, liters	2.0–2.2	2.8–3.0	1.9–2.0
Maximum voluntary ventilation			
Transpulmonary pressure, cmH_2O			
Inspiration	−(34–36)	−(58–61)	−(34–37)
Expiration	+(32–35)	+(76–89)	+(22–28)
Tidal volume, liters	2.7–2.9	1.1–1.2	2.2–2.8
MVV, liter/min	178–182	100–104	234–240
Forced expiratory flow-volume curve			
Transpulmonary pressure, cmH_2O	+(35–65)	+(140–265)	+(47–70)
Peak expiratory flow, liter/s	12.4–12.8	6.7–6.9	16.0–16.4
Resistance, cmH_2O per liter/s	2.8–5.2	20.9–39.6	2.1–4.3
Static compliance, liter/cmH_2O	0.20–0.28	0.26–0.29	0.29–0.30

Values are means for divers 5 and 6, in whom esophageal pressure was measured; similar lung volume, MVV, and flow-volume relationships were found for divers 1–4, whose esophageal pressures were not measured. All volumes corrected to BTPS.

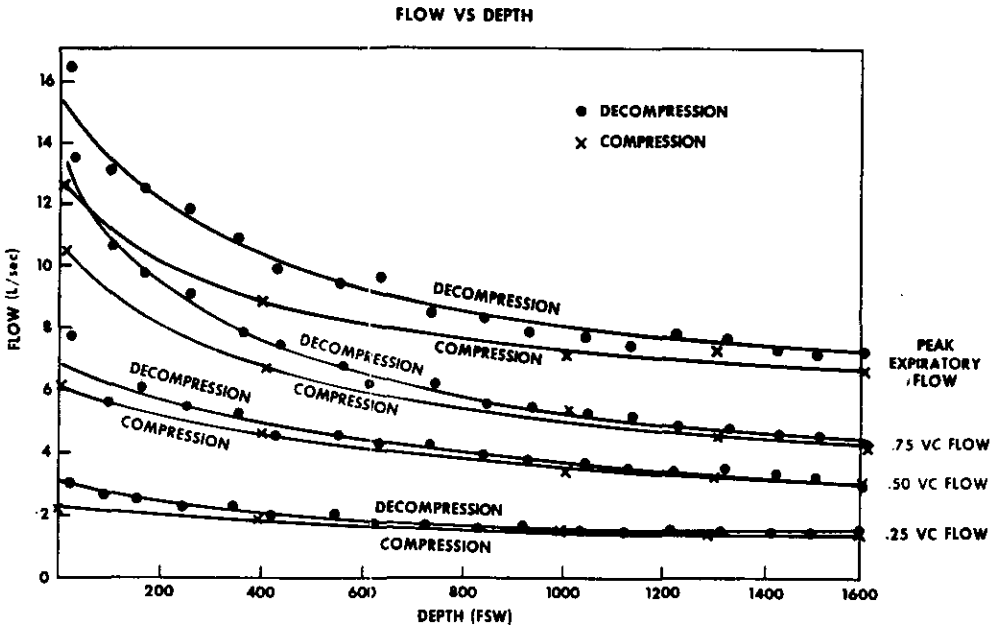

Fig. 3. Analysis of maximal expiratory flow-volume curves observed at chamber pressures equivalent to 0–1600 fsw; values are means for 6 divers.

For both inspiration and expiration, these peak pressures were about four times the respective predive values in air at 1 ATA. These measures achieved flow rates only half as great as the control values, however. Similar results were obtained with MVV maneuvers, although the divers adapted to the 49.5 ATA condition and performed MVV in a manner which differed from the predive, 1 ATA state. For example, at 49.5 ATA, they were already breathing higher in the lung volume, since expiratory reserve volume (ERV) was increased from 2.2 to 2.8 liters (Table 3). During MVV, they breathed with smaller tidal volumes (Fig. 4, V_T = 1.2 vs. 2.9 liters, predive), and tended to accumulate additional gas within the lungs in the course of the brief MVV maneuver. Peak values of transpulmonary pressure with MVV were almost twice as large as the predive control values. All variables were remeasured at the end of decompression (Table 3, $He–O_2$, 1.2 ATA). These measurements showed the expected supranormal values in $\dot{V}_E$ and MVV (Fig. 4) which would be anticipated with the respiration of a less-dense-than-air medium, such as helium with 30% oxygen at a nearly normal pressure (1.2 ATA).

In addition to the arterial blood gas determinations during immersed work, arterial P_{O_2}, P_{CO_2} and pH during supine rest were measured on repeated occasions during the 3-wk decompression from 49.5 ATA. As was true during immersed work (Fig. 2), there was no evidence of respiratory acidosis in any diver. On the contrary, the tendency was to respiratory alkalosis (Table 4), but neither arterial P_{CO_2} nor pH was systematically related to depth. These low values of resting P_{CO_2} recall the results in two subjects at 600–1500 fsw reported by Morrison, Bennett, Barnard, and Eaton (1976). The high values of arterial P_{O_2} at all depths (Fig. 5) reflected the hyperoxic chamber atmosphere. The alveolar-to-arterial oxygen difference (AaD_{O_2}) during rest ranged between 16 ± 8 (SE) and 51 ± 1 mmHg, as might be expected during hyperoxic breathing (Cole and Bishop 1967). The value of 18 mmHg at 1600 fsw agrees well with the findings of Overfield et al. (1969) from a 1000-fsw chamber dive, when the greater

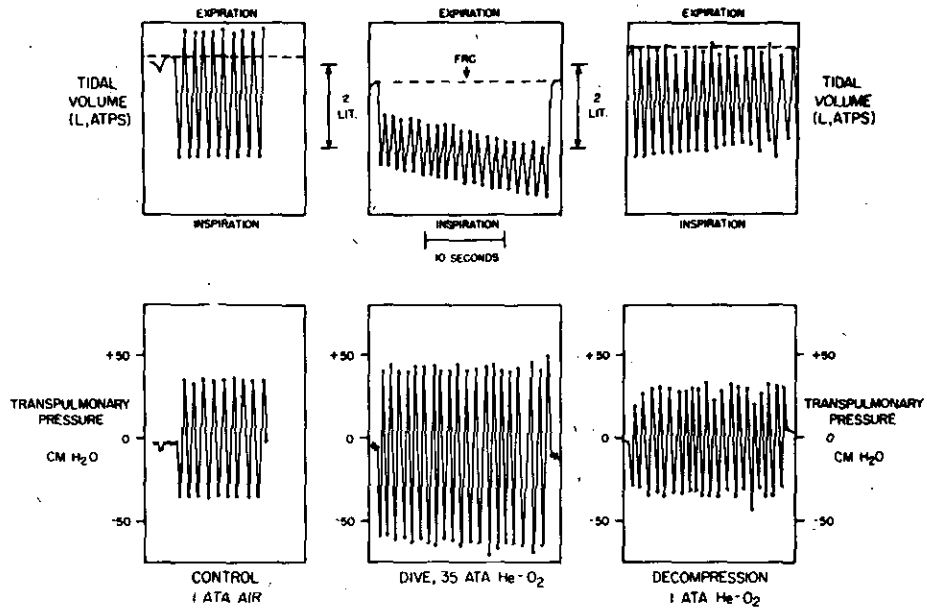

Fig. 4. Breathing pattern (tidal volume vs. time) (upper panels) and transpulmonary pressure (lower panels) during maximum voluntary ventilation (MVV). Control measurements were made in air at normal pressure (left). During MVV at 35 ATA (center), diver began MVV maneuver with an already increased expiratory reserve volume, and retained additional gas during MVV, staying progressively above functional residual capacity (FRC), shown by dashed lines, as the maneuver proceeded. The individual breaths (tidal volumes) at 35 ATA were smaller, despite greater efforts shown by wider swings in transpulmonary pressure. At end of 19-day decompression (panels at right), breathing pattern during MVV had become nearly normal. Recordings are from diver 6. Results were same at 49.5 ATA (see Table 3), but recordings did not reproduce satisfactorily.

degree of hyperoxia in this study is taken into account. Like the arterial P_{CO_2} and pH, the AaD_{O_2} was not systematically related to chamber pressure (gas density). The high value found at 1000 fsw in this study is not readily explained.

TABLE 4

Arterial P_{CO_2} and pH during supine rest as depth (chamber pressure) is decreased during 3–wk decompression from 50 ATA (1600 fsw)

Chamber Depth, fsw	1,378	1,192	1,000	808	424	232
Arterial P_{CO_2}	38 ± 1.0	39 ± 4.0	36 ± 2.0	37 ± 2.0	37 ± 2.0	34 ± 2.0
pH	7.47 ± .03	7.41 ± .03	7.42 ± .03	7.43 ± .02	7.45 ± .01	7.42 ± .01

Values are means ± SD; n = 6.

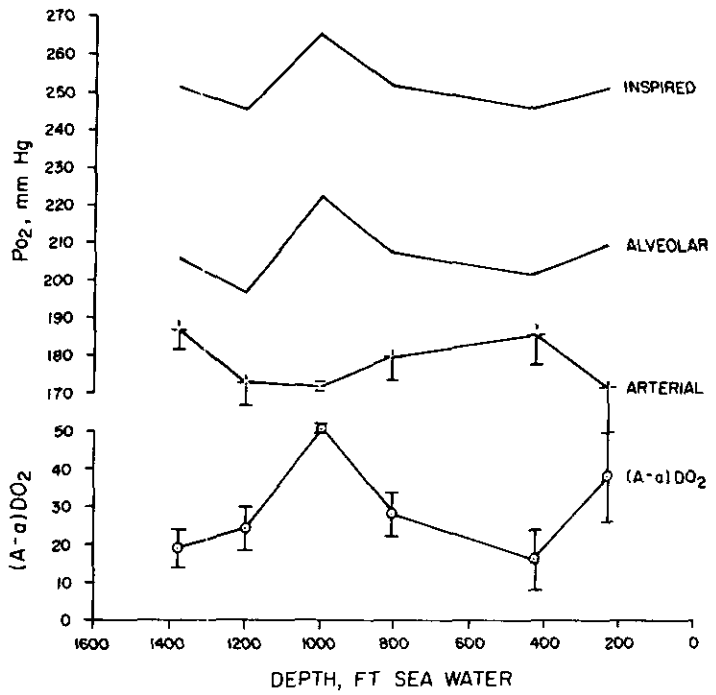

Fig. 5. Alveolar and arterial P_{O_2} in supine males undergoing decompression from 49.5 ATA maximal pressure. AaD_{O_2} was not a function of gas density (chamber pressure). Mean values (± SE) are for $n = 6$ at the three greatest depths, and for $n = 3-4$ at the lesser depths.

DISCUSSION

When diving mammals dive, the gas in their airways becomes more dense the deeper the dive. Man is no exception to this maxim, so in 1926, Sayers and Yant (1926) introduced the newly discovered light gas, helium, as a breathing medium for divers. Even with helium, however, there probably exists some limiting depth (pressure) at which gas density may render the respiratory system inadequate to support metabolic processes (Fagraeus 1974; Lanphier 1976; Lambertsen 1976). In the present study, we measured some indices of pulmonary function in the dry chamber atmosphere at 49.5 ATA and attempted to relate them to measurements of cardiorespiratory function during maximal exercise in the immersed state at the same pressure. Other, nonpulmonary, factors which might limit performance in open-sea diving were excluded by selecting experienced, healthy divers, and by providing them with comfortably warm gas and water temperatures. Hypoxia and extreme hyperoxia were also excluded. The external resistance to breathing imposed by the Mark 10 Mod 4 system was mild (Cetta and Radecki 1975). The work task was simple, employing apparatus and procedures with which the divers and investigators were familiar at lesser pressures. There is little likelihood that hemodynamic or metabolic factors were responsible for the limited exercise tolerance of the divers (Rodkey, Raymond, Collison, and O'Neal 1974; Raymond, Sode, Spaur, Uddin, Johnsonbaugh, Bauer, Knott, and Crothers 1974).

This study showed that carbon dioxide retention and its accompanying acidosis were not responsible for limiting the ability of the divers to do underwater ergometer work at 49.5 ATA. In showing that O_2 and CO_2 exchange did not limit exercise tolerance at this pressure, we

extended the observations of Overfield et al. (1969), who found no hypercapnia and only small increases in AaD_{O_2} at 31 ATA. This is in keeping with the more recent findings of Peterson and Wright (1976) and Lambertsen (1976), whose subjects appeared capable of performing greater work loads while breathing considerably denser breathing media with apparent ease. The relative limitation in our divers compared to those of Lambertsen (1976) is puzzling to us. One explanation might be a difference in work task or breathing equipment, but such would not account for the dyspnea which all 6 of our divers noticed with mild exertion or animated conversation at depths below about 1200 fsw, but which occurred in the Lambertsen subjects only at high work rates breathing $Ne-O_2$ at 1200 fsw (equivalent to $He-O_2$ at 5000 fsw). The only major difference between the two groups of subjects was age, which seems a weak explanation for such a large discrepancy in exercise tolerance.

The lack of alternative explanations for the exercise intolerance and exertional dyspnea in our divers focuses attention on possible changes in mechanics of breathing as the cause of their symptoms and reduced performance. Such changes might have resulted from either restrictive processes leading to increased lung stiffness, or from obstruction to gas flow in the lungs. With regard to the first possibility, no evidence of lung stiffness was found in the two men in whom pressure-volume curves were measured, both of whom were subjects in the exercise tests. We concluded, therefore, that structural changes in the lungs were not a factor in the limiting symptom of dyspnea in this study. Instead, dyspnea in these divers appears to have resulted from their efforts to overcome the resistance to flow of a gas seven times the density of air at 1 ATA ($He-O_2$ at 49.5 ATA). From measurements made in the dry, resting state, we inferred that the working divers were breathing higher in their lung volume, and exerting unusually great transpulmonary pressures to maintain adequate alveolar ventilation, in the face of increasing CO_2 production during work. Since it was not possible to measure esophageal pressures in the divers while they worked underwater at 49.5 ATA (they were already encumbered with underwater breathing apparatus, radial artery cannulation, and electrocardiographic leads), we recognize that our esophageal pressures from the $\dot{V}$/Vol and MVV maneuvers provide only indirect assessment of what happened to lung mechanics during immersed exercise. However, the fact that the qualitative impairment, less flow despite greater driving pressure, was the same in both the $\dot{V}$/Vol and MVV measurements, makes it reasonable to suppose that these maneuvers offer a useful insight into the origin of the divers' dyspnea during immersed exercise. Clearly, if the men breathed during work as they did during the MVV maneuvers (Fig. 4) marked dyspnea would be expected to impair function at least as rapidly as what we observed. Additional studies with more detailed measurements of lung mechanics during exercise should help clarify some of the questions raised by the present observations.

Results of spirometric measurements

The high gas density encountered at the maximum chamber pressure in this study was expected to reduce gas flow rates in the airways in accordance with the findings of Schilder, Roberts, and Fry (1963). Since their study, others have made observations on the changes in $\dot{V}$/Vol relationships caused by increased density. For example, Broussolle, Chouteau, Hyacinthe, Le Pechon, Burnet, Battesti, Cresson, and Imbert (1976) included such measurements in a chamber dive similar to ours, but at a greater pressure. The $\dot{V}$/Vol changes in our divers (Fig. 6) are quite similar to those which they reported. In a more elaborate study of $\dot{V}$/Vol, Anthonisen, Bradley, Vorosmarti, and Linaweaver (1971) varied both pressure and gas composition to yield relative densities (air, 1 ATA = 1.0) from 0.4 to 15.0. Interpolating among their high-density values, we again note substantial agreement of our data with theirs.

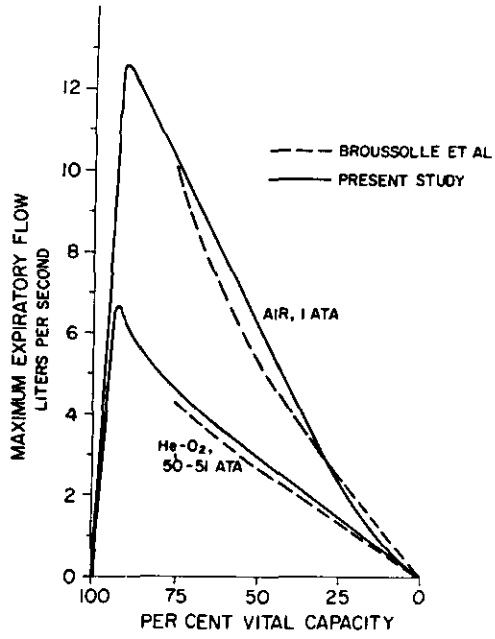

Fig. 6. Comparison of flow-volume ($\dot{V}$/Vol) relationship, air at 1 ATA vs. $He-O_2$ at 49.5–51 ATA. There was close agreement between present (n = 6) results and those of Broussolle et al. (1976) (n = 2).

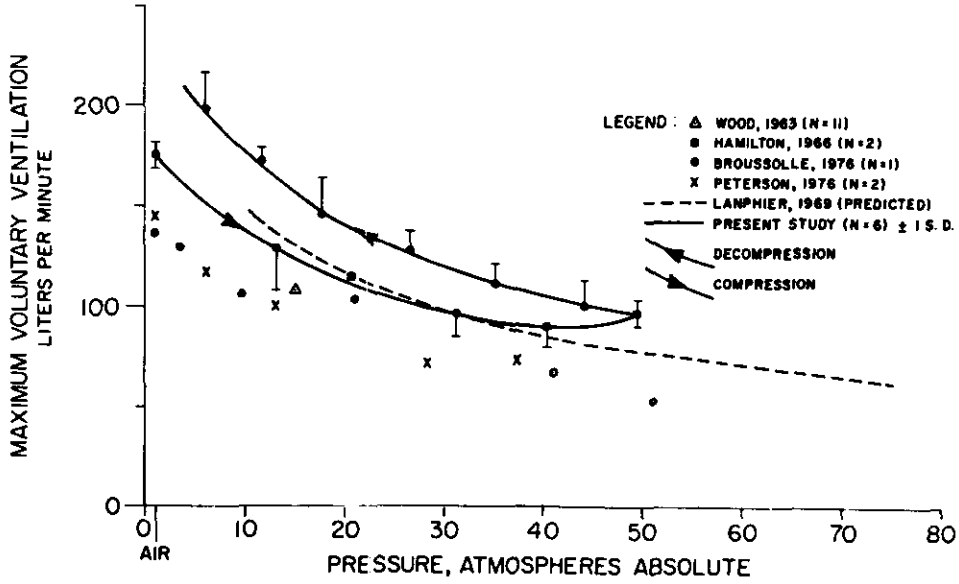

Fig. 7. Reduction in MVV with increasing pressure (adapted from Lanphier (1976)). Hysteresis, higher values during decompression than during earlier, compression measurements, probably reflects a training effect; values are means ± SE for n = 6.

MVV has been measured in a larger number of studies over a wide range of pressures and gas densities. The use of MVV as an index of pulmonary function can be criticized on a number of grounds, of course, but it should probably continue to be measured in studies such as this, since it provides continuity among diverse sets of observations. In our divers, MVV decreased as a hyperbolic function of ambient pressure in a manner similar to the initial predictions of Lanphier (1976), which have recently been reviewed. Similar results were more recently reported by others (Broussolle et al. 1976; Peterson and Wright 1976). A direct comparison of the results of MVV measurements by different groups is made difficult by discrepancies in age, size, training, and other characteristics of the subjects and equipment used in testing. For example, not all reports give control (air, 1 ATA) data for comparison. Nevertheless, it is apparent that a similar hyperbolic fall-off in MVV with increasing ambient pressure has been shown by most of the $He-O_2$ studies (Fig. 7). An unexpected finding in the present study was that of hysteresis in the MVV-depth relationship such that MVV values for any given depth were higher in the decompression phase of the dive than for the initial measurement. Most of this increase in MVV is probably attributable to training (Leith and Bradley 1976), but other factors cannot be excluded.

Relationship between MVV and exercise ventilation

The relationship between MVV and *minute volume of ventilation* ($\dot{V}_E$) *during exercise* should also be considered. This relationship is not clearly established for man at 1 ATA. Since MVV is a brief, somewhat exhausting maneuver, it is obvious that ventilation at this level can not be long sustained (Leith and Bradley 1976). While the actual ratio of maximal exercise-$\dot{V}_E$ to MVV is therefore less than 1.0, the actual values vary quite widely (Fagraeus 1974; Lanphier 1976). Like Broussolle et al. (1976), we wished to estimate the ratio of $\dot{V}_E$ during maximal exercise to MVV in our divers. To do so required a few assumptions, since $\dot{V}_E$ was not measured directly in this study. First, it was assumed that $\dot{V}_{CO_2} = \dot{V}_{O_2}$ (respiratory exchange ratio = 1.0), as is usually true with moderate exercise associated with a small rise in lactate production. If one also assumes that alveolar P_{CO_2} is equal to the measured arterial P_{CO_2}, then one can solve equation (1) for the value of alveolar

$$\dot{V}_A = 863 \cdot \frac{\dot{V}_{CO_2}}{P_{A\ CO_2}} \quad (1)$$

ventilation, $\dot{V}_A$. In our divers at the limit of exertion, we found $\dot{V}_{CO_2} = 1.9$ liter/min STPD, and $P_{aCO_2} = 36$ mmHg (the constant 863 is needed to yield values of $\dot{V}_A$ in BTPS units), and thus computed $\dot{V} = 45$ liter/min, BTPS. Since $\dot{V}_E = \dot{V} + \dot{V}_D$, we computed $\dot{V}_D$ from the observed respiratory rate and an assumed dead space ($\dot{V}_D = 400$ ml), such that $\dot{V}_D = 29 \times 0.4 = 12$ liter/min, and $\dot{V}_E = 57$ liter/min, BTPS, at 49.5 ATA. This value of $\dot{V}_E$ turns out to be about 56% of MVV at the same pressure (mean MVV = 102 liter/min).

From the data reviewed by Lanphier (1976), this level of $\dot{V}_E$, expressed as a percentage of the MVV, can probably be sustained for only about 15 min under optimal conditions. One must then recall that MVV in our study was measured with only the imposed resistance of the measuring apparatus, a balanced wedge spirometer. For the immersed diver with his suit, surrounding water and Mark 10 breathing equipment, even though the measured breathing-resistance was low, it seems reasonable to expect that the duration for which $\dot{V}_E$ could be

sustained at 50–60% of MVV might be considerably less than 15 min, although we did not make direct measurements of duration in this study. However, we believe that the limitation to exercise in our divers was one of mechanical origin, related to the work of breathing.

The precise source of such limitation is not clear, however. The main possibilities seem to be as follows. First, there is the tendency of the divers to breathe at abnormally high lung volumes (Fig. 4), resulting in the addition of elastic loading superimposed on a recognizably high resistive impedance. A second possibility is that the high density of the breathing mixture resulted in intense stimuli from shearing or impaction forces (or both) on mucosal surfaces, especially during exercise. A corollary of this idea is that respiratory muscles were subjected to unaccustomed loads at maximal levels of exercise, and they responded by generating adverse stimuli. A third notion is similar to the first two but deals with a more elusive proposition: that perfusion of the respiratory muscles becomes inadequate in these unusual circumstances to support the unique metabolic requirements of the high resistive and elastic loads of these experimental conditions. The design of the present study does not allow us to choose among these (and other) possibilities, but the results seem vulnerable to further experimental attack.

Perspective

The physiological changes exhibited by the divers include some of the adjustments seen in acute attacks of bronchospasm in asthmatic humans (Permutt 1973). These include hyperinflation, dyspnea in the absence of hypoxemia or CO_2 retention, impaired flow rates, and increased pulsus paradoxus. In regard to the clinical diagnosis of asthma or exercise-induced bronchospasm, we point out that auscultation of the chest on repeated occasions before and after exercise showed no evidence of airway dysfunction. Whether the similarities of the responses in our divers to dense gas breathing vis-a-vis those of asthmatics are merely coincidental or are indicative of a similarity in mechanism at some level must remain a matter of continuing inquiry. "For a long time, it has been assumed that the increase in density of the respired gases might be a limiting factor in underwater exploration"(Varene, Vieillefond, Lemaire, and Saumon 1974). We agree that density may limit underwater performance, though the mechanism of the limitation remains unclear. Uncertainty in this regard, however, will serve as a catalyst rather than a damper for further study, at least for the physiologist and diving medical officer.

We thank the divers, corpsmen, technicians, and other co-workers of the U.S. Navy and of Taylor Diving and Salvage Co., Belle Chasse, LA, who contributed to the safe completion of these experiments. The study was supported by the Supervisor of Diving and the Bureau of Medicine and Surgery, U.S. Navy, under Research Work Unit M4306.02.6010BAK9. The opinions in this paper are those of the authors and do not necessarily reflect the views of the Navy Department or the naval service at large.—*Received for publication August, 1976; revision received January, 1977.*

Spaur, W. H., L. W. Raymond, M. M. Knott, J. C. Crothers, W. R. Braithwaite, E. D. Thalmann, and D. F. Uddin. 1977. La dyspnée du plongeur à 49,5 ATA: d'origine mécanique plutot que chimique. Undersea Biomed. Res. 4(2): 183–198.—La fonction pulmonaire a été étudiée chez 6 plongeurs qui habitaient une chambre hyperbare à une pression à peu près 50 fois la normale (49,5 ATA = 488 m = 1600 fsw). Comme de raison, la fonction ventilatoire a diminué. A 49,5 ATA, la ventilation volontaire maximale était de 45% moindre que la valeur témoin. Les vitesses instantanées de débit de gaz pendant la respiration forcée étaient aussi réduites, surtout les vitesses

mesurées pour les volumes pulmonaires plus grands. Ces réductions se sont produites malgré une *augmentation apparente* de la capacité fonctionnelle résiduelle, et l'emploi de pressions transpulmonaires supérieures à celles qu'on observe au cours des mêmes exercises à une pression normale (au niveau de la mer). Pendant le travail subaquatique, les sujets se sont fatigués rapidement à des *taux de consommation d'oxygène modérés* (1,9 l/min); la fatigue était accompagnée d'une dyspnée importante et de la syncope imminente. Nous n'attribuons pas ces symptômes à la retention de CO_2, ni à des causes hemodynamiques ou métaboliques, mais plutot à la respiration d'un gaz dense, *ce qui représente, avec l'asthme, une condition* dans laquelle peut survenir une dyspnée importante accompagnée d'un taux normal ou même sous-normal de CO_2 artérielle et un transport d'oxygène normal. Les adaptations physiologiques employées par les plongeurs ressemblent à celles qu'on *observe chez l'asthmatique aigu. Les hommes peuvent* accomplir un travail modeste sous les conditions de cette expérience, mais la réserve physiologique, qui permettrait aux plongeurs de faire face aux urgences ou aux infections respiratoires éventuelles, se trouve diminuée.

asthme	exercise
dioxyde de carbone	hélium

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Effect of increased ambient pressure on flow-volume curve of the lung

L. D. H. WOOD AND A. C. BRYAN
Canadian Forces Institute of Environmental Medicine, Toronto 12, Ontario, Canada

WOOD, L. D. H., AND A. C. BRYAN. *Effect of increased ambient pressure on flow-volume curve of the lung.* J. Appl. Physiol. 27(1): 4–8. 1969.—Maximum expiratory flow (MEF) has been measured at six lung volumes in eight healthy subjects at 10 ambient pressures from 1.0 to 10.0 atmospheres absolute. MEF varied as density$^{-0.45}$ at lung volumes greater than 25% of VC and became less density dependent at lower lung volumes. Theoretical calculations based on the equal pressure point concept have been made, showing that if all flow in the upstream segment were turbulent, MEF would vary as $\rho^{-.45}$ to $\rho^{-.50}$. It was concluded that most of the flow in the upstream segment is nonlaminar at lung volumes greater than 25% of vital capacity. A flow regime is advanced to explain this conclusion in the light of the very low Reynolds numbers. One explanation for carbon dioxide accumulation in the working deep diver is advanced.

lung mechanics; hyperbaric physiology; maximum flow-volume curve of the lung; equal pressure point concept; small airway flow regime; CO_2 accumulation in diving

AS A RESULT OF THE SUBJECTIVE sensation of increased difficulty in breathing at increased ambient pressure, investigations into the pressure-flow relationships of gases of increased density have been carried out (10, 12, 14, 17, 18). In general, observations have been made that maximum breathing capacity and peak expiratory flow vary inversely and apparently exponentially with the density of the air. Miles (14) observed that maximum breathing capacity varies inversely as the square root of the density and offered an explanation based on the mass-velocity equation:

$$P \approx \tfrac{1}{2}M\dot{V}^2$$

where P = the work done during breathing, M = the mass, $\dot{V}$ = flow. He assumes the work of breathing to be constant at every depth, so flow varies inversely as the square root of mass, and mass is directly proportional to density.

We have felt that a more precise explanation of the relationship between expiratory airflow and density may be provided. In this study, we have used maximum expiratory flow-volume (MEFV) curves to measure maximum expiratory flow at six lung volumes, and to determine the effect of increased ambient pressure on these flow rates. We have used the equal pressure point concept of Mead et al. (13) to explain the observed relationship between maximum expiratory flow and density of gas breathed.

METHODS AND MATERIALS

The subjects for this experiment were eight Canadian Armed Forces divers (Table 1). Each subject contributed from four to six MEFV curves at each of 10 different ambient pressures from 1 to 10 atmospheres absolute (Ata).

The MEFV curves were obtained with the method of Hyatt, Schilder, and Fry (6, 8). The subjects expired from total lung capacity to residual volume into a wedge spirometer (Med-Science Electronics model 270), and the flow and volume signals were displayed on the ordinate and abscissa of a storage oscilloscope (Tektronix type 564). Each subject performed three to five expirations of varying effort, the first being maximum and subsequent effort being guided by the recorder in such a way as to provide the maximum perimeter of the flow-volume curve. This maximum perimeter was copied from the oscilloscope using a mirror system and maximum expiratory flow measurements were made at six lung volumes (Fig. 1). Approximately 50 data points for each subject at each lung volume were obtained. These were plotted against density, and lines of visual best fit were drawn through the data.

All expiratory maneuvers were performed in the hyperbaric chamber at the Defense Research Establishment, Toronto. The frequency response of the wedge is quoted by the manufacturers to be flat for flow and volume through 22 cycles/sec. The wedge resistance was measured at 1.0, 7.0, and 10.0 Ata and did not vary significantly.

Isovolume pressure-flow curves were obtained from one subject at 1.0 and 10.0 Ata. Flow and volume signals were obtained from the wedge spirometer. Esophageal pressure values were obtained with a rubber balloon (length 10 cm, perimeter 4.0 cm, wall thickness ca. 0.06 mm) sealed over a polyethylene catheter (id 0.15 cm, od 0.21 cm, length 90 cm) with spirally arranged holes connected to a pressure transducer (Sanborn model 267B). Pressure, volume, and flow were simultaneously displayed on a Sanborn direct-writing oscillograph.

RESULTS

The data for each individual, plotted as maximum expiratory flow at each measured lung volume against density in atmospheres absolute, form a family of curves (Fig. 2). The same data plotted logarithmically become a family of straight-line relationships (Fig. 3), whose mathematical description is seen at the left of each line. The equation has

TABLE 1. *Vital statistics and lung volumes*

SUBJECT	AGE yrs	HT (cm)	WT (Kg)	TLC (l)	% RV/TLC	% FRC/TLC
K.P.	40	168	63.9	5.0	24.0	42.0
K.W.	35	170	95.2	6.2	27.4	42.0
B.O.	30	175	90.7	5.9	28.8	51.0
L.S.	29	168	74.8	5.3	22.3	45.4
J.W.	38	180	97.5	7.5	36.0	48.0
A.B.	39	178	79.8	6.5	26.2	56.0
C.K.	36	170	73.5	7.0	25.8	46.0
L.W.	25	180	83.9	8.3	26.5	54.0
MEAN	34.0	176	84.9	6.5	27.1	47.8
S.D. (N=8)	±5.4	±5.2	±8.9	±1.1	±4.1	±4.8

Lung volumes are corrected to BTPS. Residual volume was measured by nitrogen washout.

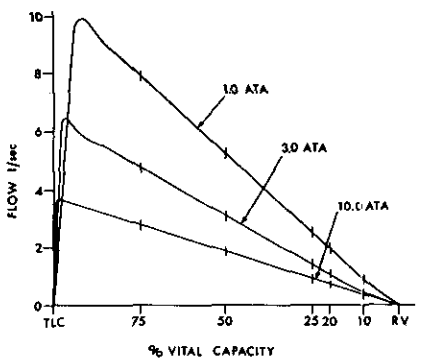

FIG. 1. MEFV curves for one subject measured at 1.0, 3.0, and 10.0 Ata. Maximum flow measurements were made at the five indicated lung volumes and at peak flow. MEFV curves were obtained for all subjects at 10 ambient pressures and each subject contributed four to six MEFV curves at each depth.

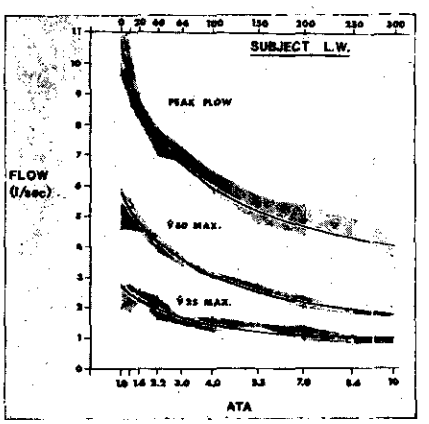

FIG. 2. Maximum flow values for one subject at three different lung volumes plotted against air density, expressed in Ata. At the top are the equivalent depths in feet of seawater. Measurements were made at the nine indicated depths and at 1.3 Ata (10 ft). Shaded area shows the range of measured values. Number of data points at each lung volume range between 40 and 50 for all subjects. Solid line is the line of best fit.

the basic form: $Y = K x^n$. The exponent in each equation is the slope of the line and so describes the relationship of flow to density. K describes the flow value at a density of 1.0 Ata. The shaded area depicts the range of measured values. Table 2 shows the slopes and K values at each lung volume for each subject.

Our results show an exponential decrease in maximum expiratory flow with increasing density. At 25, 50, and 75% of vital capacity, the exponent ($\rho^{-.43}$ to $\rho^{-.46}$) approximates a root function ($\rho^{-.50}$), i.e., MEF varies approximately inversely as the square root of the density.

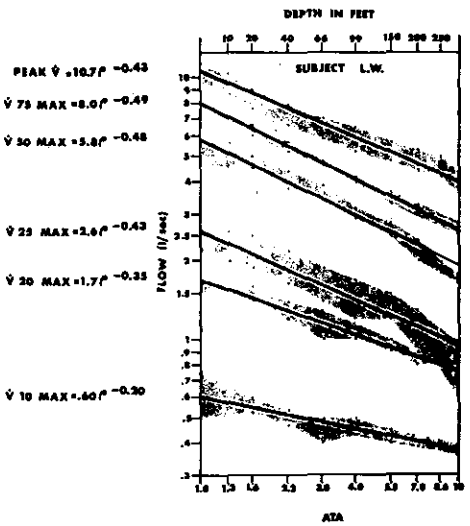

FIG. 3. Logarithmic plot of maximum expiratory flow at six lung volumes against air density for one subject. Shaded area shows the range of measured values. Equations at the left describe the adjacent solid lines of visual best fit, i.e., $\dot{V}_{75}$ max is the maximum flow at 75% of vital capacity. Exponent is the slope of the line, and so describes the relationship of maximum expiratory flow to density at that lung volume. The decreasing slope with decreasing lung volume is shown.

TABLE 2. *Slopes (N)* and constants (K) for all subjects at each lung volume, derived from a logarithmic plot of MEF against ρ for each subject*

	MAX. EXP. FLOW Vs DENSITY											
SUBJECT	PEAK FLOW		% LUNG VOLUME									
			75		50		25		20		10	
	N	K	N	K	N	K	N	K	N	K	N	K
K.P.	.38	4.4	.45	4.5	.42	2.6	.36	.94	.19	.46	.13	.20
K.W.	.41	9.1	.51	7.6	.45	4.1	.49	1.7	.40	1.1	.38	.39
B.O.	.41	9.2	.43	7.0	.45	4.6	.48	2.0	.37	1.3	.14	.41
L.S.	.43	9.6	.50	7.0	.46	3.9	.43	1.7	.39	.98	.29	.33
A.B.	.35	9.8	.45	7.3	.43	5.0	.37	2.2	.35	1.6	.24	.52
J.W.	.45	10.4	.42	6.9	.43	4.0	.38	1.6	.27	.94	.11	.32
C.K.	.42	10.6	.42	7.8	.48	5.4	.45	2.4	.27	1.2	.16	.53
L.W.	.43	10.7	.49	8.0	.48	5.8	.43	2.6	.35	1.7	.20	.60
MEAN	.41	9.5	.46	7.0	.45	4.4	.43	1.9	.32	1.2	.20	.42
S.D. (N=8)	±.03	±1.4	±.04	±1.1	±.02	±1.0	±.05	±.53	±.07	±.39	±.09	±1.3

* All slopes are negative.

DISCUSSION

Lord, Bond, and Schaeffer (10), using a similar experimental method, demonstrated a family of curves at different lung volumes plotting flow versus density. We have replotted logarithmically the data of Wood, Leve, and Workman (18), which show that maximum expiratory flow varied as density$^{-0.45}$ and maximum breathing capacity varied as density$^{-0.48}$. Marshall, Lanphier, and DuBois (12) observed that flow rates are halved at 4 Ata. Miles (14) had previously observed that MBC varies inversely as the square root of density and offered an explanation based on the equation of kinetic energy.

Mead and colleagues (13) have demonstrated the unique relationship between static recoil pressure of the lung and maximum expiratory flow. Figure 4 shows the essential features of this concept as it applies to our data. Alveolar pressure (Palv) is the driving pressure of expiratory airflow. It exceeds pleural pressure (Ppl) by an amount equal to the static recoil pressure of the lung (Pst(l)). During maximum expiratory flow, there is a pressure drop along the intrathoracic airways which at some point equals the static recoil pressure of the lung, such that intraluminal and extraluminal pressures are equal to Ppl. These equal pressure points (EPP) *divide the airway into two segments in series.* The upstream segment in each individual is characterized by a fixed driving pressure Pst(l) and a fixed geometric configuration of the airways at each lung volume. The pressure drop in the upstream segment equals Pst(l) and has two components: *i*) the frictional pressure losses, Pfr, composed of turbulent (Ptu) and laminar (Pla) *pressure drops, and ii*) pressure losses due to convective acceleration (Pca). This latter term refers to the energy required to accelerate gas particles between two points with converging boundaries, or the Bernoulli effect. The formulas for each of these is approximately known (7):

$$\text{Pca} = K\frac{\rho\dot{V}^2}{2g\ \text{DEPP}^4} \qquad (1)$$

where ρ = density, $\dot{V}$ = flow, g = gravity, DEPP = diameter of the EPP, and K is a constant. It is seen that if the pressure drop along the upstream segment were completely due to convective acceleration, then maximum expiratory flow would vary as density$^{-0.50}$ (13).

$$\text{Ptu} = \frac{\rho^{.75}\eta^{.25}\dot{V}^{1.75}}{D^4} \qquad (2)$$

where η = *viscosity and* D = *diameter.* This empirical equation describes the pressure drop accompanying turbulent flow in smooth-walled tubes and predicts that if Ptu were equal to Pst(l), the maximum expiratory flow would vary as density$^{-0.43}$. The equation changes with increasing roughness of the walls such that the relationship of maximum expiratory flow to density tends towards that of *equation 1*, i.e., maximum expiratory flow varies as $\rho^{-0.50}$.

$$\text{Pla} = \frac{8L\eta\dot{V}}{D^4} \qquad (3)$$

It follows that if laminar flow accounted for the whole pressure drop along the upstream segment, maximum expiratory flow would be independent of density.

If all the flow in the upstream segment were turbulent, maximum expiratory flow would vary between density$^{-0.43}$ and density$^{-0.50}$. As the proportion of laminar flow increases maximum flow would become less density dependent, i.e., the exponent would become smaller. The observed relationship between maximum expiratory flow and density at lung volumes greater than 25% of vital capacity conforms to this predicted relationship, provided laminar flow contributes minimally to resistance in the upstream segment. As lung volume decreases below 25% of vital capacity, our data suggest that laminar flow becomes an increasingly large component of the flow regime. This conclusion is supported by the work of Schilder, Roberts, and Fry (17) who have shown that altering the viscosity of an expired gas affects maximal expiratory flow only at lung volumes less than 25% of vital capacity. Further support is provided by the considerations of Mead et al. (13) who have pointed out that the shape of the flow-volume curve suggests that those pressure drops along the upstream segment which are pro-

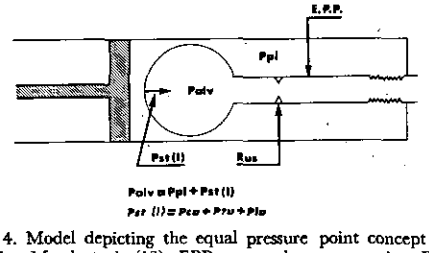

FIG. 4. Model depicting the equal pressure point concept of the lung after Mead et al. (13). EPP = equal pressure point; Palv = alveolar pressure; Ppl = pleural pressure; Pst(l) = static recoil pressure of the lung; Rus = resistance of the airway upstream from the EPP; Pca = pressure drop due to convective acceleration; Ptu = pressure drop due to turbulent flow; Pla = pressure drop due to laminar flow.

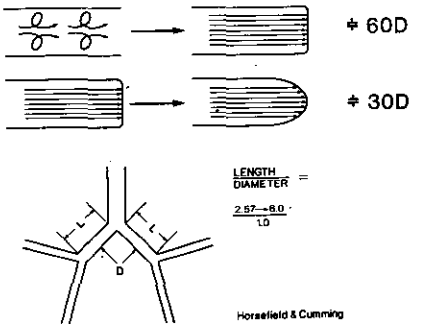

FIG. 5. L = length of airway segment between branches; D = diameter of the segment. Hypothetical flow regime in the small airways. Distances required for flow in each segment to become laminar are considerably greater than the measured lengths, suggesting that *true laminar flow is rare* despite the very low Reynolds numbers.

portional to $\dot{V}^2$ (i.e., Pca and Ptu) will decrease more rapidly than the pressure drop proportional to $\dot{V}$ (i.e., Pla) as lung volume decreases. Thus, Pla will account for a greater part of the total pressure drop as lung volume decreases.

A transition from turbulent to laminar flow at low lung volumes might be predicted on the basis of decreasing Reynolds numbers associated with the decrease in flow. However, the available data show Reynolds numbers in the upstream segment to be considerably below critical values even at high flow rates (2, 15). To explain our finding of considerable density-dependent flow in the upstream segment we suggest the following flow regime, the essentials of which are depicted in Fig. 5.

We assume that air flowing from the alveoli toward the equal pressure point will be disturbed, particularly at each point of branching where there are converging airstreams and redirection of flow (15). Even in the presence of extremely low Reynolds numbers a distance is required for transition of these vortices of turbulence to laminar flow. This distance has been estimated for flow in smooth-walled tubes at approximately 60 diameters of the tube (16). In addition, laminar flow enters each new branch with a blunt profile, and energy, i.e., pressure, is required to produce a parabolic profile. Until this profile is established the pressure drop is described by a modification of Poisseuille's law (16), *equation 4*:

$$P = \frac{8L\eta\dot{V}}{D^4} + \frac{\rho\dot{V}^2}{2D^4} \qquad (4)$$

The distance required for this transition has been estimated at 30 times the diameter of the tube in smooth-walled vessels (16). The airstream must pass approximately 20 branches from the alveolus to the equal pressure point. The length-diameter relationship of each segment of the airway has been measured at 2.57:1 in the terminal bronchioles increasing to 6.0:1 in the larger airways (4). It follows that most of the airflow is in transition from the turbulent vortices to laminar flow and from laminar flow with a blunt profile to laminar flow with a parabolic profile, i.e., despite the low Reynolds numbers true laminar flow must be rare. The mathematical description of this pressure drop would be a complicated algebraic sum of *equations 1, 2,* and *4*, explaining the observed density relationship in the absence of critical Reynolds numbers.

The density dependence of expiratory flow could also be explained if the convective acceleration is greater than the frictional component. In this case flow would vary as $\rho^{-0.5}$ regardless of the flow regime (*eq 1*). Macklem and Mead (11) have shown in excised human lungs that the component of upstream resistance due to convective acceleration is greater than the frictional component at lung volumes above 60% VC. However, the continued density dependence of flow at lower lung volumes where frictional resistance is dominant must mean that flow is not laminar despite the very low Reynolds numbers.

Agostoni and Fenn (1) have demonstrated that maximum flow at high lung volumes is limited by the velocity of muscle shortening. These effort-dependent maximum flow rates at high lung volumes are lower than would occur if the subject were able to generate enough pleural pressure to produce an effort-independent maximum flow. If we assume that the velocity of muscle contraction does not change in going from 1.0 to 10.0 Ata, it follows that in the time required to generate positive pleural pressure sufficient to produce a fixed equal pressure point, there will be less change in lung volume at the deeper depth, i.e., effort independence of maximum flow rates will occur at higher lung volumes as air density increases. This explains, in part, why peak flow occurs at higher lung volumes as air density increases (see Fig. 1). Since at depth we achieve peak flow rates determined by the equal pressure point and the flow-limiting segment, whereas closer to the surface we fall short of these maximum flow rates, the observed relationship of maximum expiratory flow to density becomes less than predicted by the equal pressure point concept at high lung volumes. As shown in Table 2, peak flows vary as density$^{-0.41}$, a lesser density dependence than at 75, 50, and 25% of vital capacity.

The wedge spirometer has been shown to be less accurate than a body plethysmograph in relating flow to volume events in the lung because measurement of volume change at the mouth ignores the effect of intrathoracic gas compression, and so overestimates thoracic volume (8). Maximum perimeter flow-volume curves have been used to obviate the problem of gas compressibility and have provided maximum flow-volume curves almost identical to body plethysmograph curves in subjects free of obstructive lung disease. In addition, the error due to gas compression can be expected to decrease as ambient pressure increases. It is apparent that some or all of the variability of flow values for each lung volume in each individual is due to this method of determining the maximum flow-volume curve.

These mechanical limitations may be a major factor in the genesis of the CO_2 retention that is known to occur under pressure (9). Figure 6 shows the flow-volume curve and isovolume pressure-flow curves of one subject measured at 1 and 10 Ata. Expiratory flow during moderate exercise is very close to his maximum flow at depth. At the surface, ventilation can be increased by a small increase in pleural

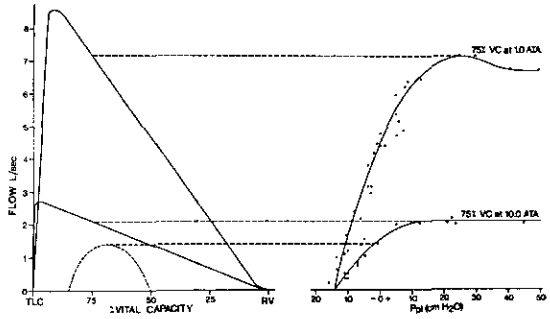

FIG. 6. MEFV curves for one subject at 1.0 and 10.0 Ata and the corresponding isovolume pressure-flow curves at 75% of vital capacity. Expiratory flow-volume loop superimposed on the MEFV curves shows that, for a given ventilation, the subject is much closer to his maximum flow plateau at the deeper depth.

pressure. At depth, a similar increase in ventilation requires a greater increase in pleural pressure (i.e., work) and further increases in ventilation are sharply limited by the plateau of the isovolume pressure-flow curves. A vicious circle could be established during exercise by an increased work of breathing without an attendant increase in ventilation leading to carbon dioxide accumulation. This hypothesis was previously advanced by Fry and Hyatt (3) to explain the precipitous deterioration of emphysematous patients subjected to minor respiratory insults. It would seem that the emphysematous patient and the healthy diver at depth are similar in that the resting ventilation of both are very near the flow plateaus of their isovolume pressure-flow curves.

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