Key Documents of the Biomedical Aspects of Deep-Sea Diving

SELECTED FROM THE WORLD'S LITERATURE
1608–1982

Volume III

GAS EMBOLISM

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GAS EMBOLISM

T. G. SHIELDS

The subject of cerebral arterial gas embolism (AGE) has been reviewed recently by Peirce (1980) in a comprehensive but admirably concise paper which provides an excellent entry into the literature.

It is only in the last twenty years or so that the distinction has been made between AGE secondary to barotrauma and neurological decompression sickness (DCS) as wholly separate dysbaric illnesses. It is clear that earlier studies of the aetiology of neurological DCS have been complicated by the inclusion of unrecognised cases of "burst lung."

The difference between AGE and neurological DCS was first clearly delineated by two U.S. Navy physicians, Drs. Polak and Adams (1932) who investigated in dogs the pressure required to rupture the stretched alveolar walls and drive air into the circulation. This work was confirmed by Schaefer et al. (1958); and was extended to fresh human cadavers by Malhotra and Wright in 1961.

Earlier research into the mechanisms and effects of AGE was not related to diving and came largely from the clinical fields of neurosurgery and cardiopulmonary medicine. An excellent early review of the condition quoting clinical observations supplemented by experimental work on dogs was provided by van Allen et al. in 1929. In 1944 Macklin and Macklin published a highly detailed study of the fundamental concepts involved in expansion rupture of the lung. More recently, still outside the strictly diving context, de la Torre et al. (1962) looked closely at the mechanisms of intracranial air injection in dogs and demonstrated conclusively the very small quantity of intra-arterial gas necessary to produce a pathological response. They emphasised the importance of the choice of experimental animal in this type of work and also pointed out the difference in effect between solid embolisation (mainly hemorrhagic) and embolisation with gas (primarily ischaemic).

Perhaps the most important recent advance in understanding the pathology of the condition is the growing realisation of the possible development of cerebral oedema as a sequel to cerebral AGE and the demonstration by Hallenbeck and coworkers (1977) of secondary haematological effects, microvascular damage, and the problems of reperfusion of the ischaemic area.

Reviewers of clinical cases of AGE (for example, Greene, 1978) have suggested that sudden death might be due to myocardial involvement. Possible mechanisms have been summarised by Evans et al. (1977), but the question of a neurogenically-mediated response to direct embolisation of the coronary vessels remains unresolved.

Early attempts at therapy were simply on the basis of deep recompression to eliminate the embolising bubble. The efficacy of this was clearly demonstrated (in dogs) by Waite et al. (1967) using a cranial window technique. A reappraisal of this approach was made by van Genderen and Waite in 1968 in an attempt to reduce treatment time, incidence of residual symptoms and the apearance of DCS attributable to the therapy. The outcome of this work was the currently accepted USN Table 6A. This "hybrid" table, relying as it does more on hyperoxia than on pressure per se, was a happy choice. Hyperbaric oxygen is one of the most powerful anti-cerebral-oedema agents available. Its use, together with adjuvant drug therapy indicated by the continuing work of Hallenbeck, has permitted a more rational and aggressive approach to therapy in this potentially lethal condition.

GAS EMBOLISM

T. G. SHIELDS

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de la Torre E., Meredith J., Netsky M. G.: Cerebral air embolism in the dog. *Arch Neurol* 1962; 6:307–316. Copyright 1962, American Medical Assoc.

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ARCH. NEUROL. 6:307-316

Cerebral Air Embolism in the Dog

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The problem of air embolism has attracted the attention of many investigators. The literature contains numerous reports of severe neurologic damage or unexpected death occurring during some types of thoracic or abdominal diagnostic and therapeutic procedures.[2,4,5,8,21] More recently, operations in the neck during cordotomy, laminectomy, and thyroidectomy have been blamed for air embolization with subsequent neurologic deficits or death.[19-21] Obstetricians and gynecologists also have encountered the problem in patients during postpartum knee-chest exercises.[28] Interest in the danger of air embolism has increased since the advent of open-heart surgery and the use of the artificial oxygenator.[24]

Experimentally, the effects of air emboli differ greatly, depending on whether they are "venous" (injection usually in femoral or jugular vein) or "arterial" (injection in carotid artery or pulmonary vein). In the case of "venous" embolization, large amounts of air are tolerated by experimental animals, perhaps because of the filtering effect of the pulmonary barrier.[3,12,33] Pulmonary hypertension occurs because the circulation in the pulmonary circuit is obstructed. A "mill-wheel sound" is heard over the chest when air bubbles are trapped in the right side of the heart. The consequent diminished amount of blood in the left side of the heart accounts for systemic hypotension. Villaret and Cachera[33,34] indicated that air still can pass to the general circulation in some

Received for publication Sept. 5, 1961.

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Supported in part by research grants B-1088 and B-2417 from the National Institute of Neurological Diseases and Blindness, and H-4655 from the National Heart Institute, U.S. Public Health Service.

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animals through a patent foramen ovale, with a concurrent rise in pressure in the right side of the heart.

In "arterial" embolization, air injected into the pulmonary vein can pass either toward the coronary or the cerebral circulation, depending on the position of the subject.[9,13,29,32,33,35] Air emboli pass to the brain in the head-up position, to the heart in the head-down position. A slight increase in blood pressure is reported in cases of cerebral embolization, perhaps because of increased peripheral resistance. If embolization is not massive, or if it occurs slowly, the air emboli pass through the capillary system in a few minutes, without permanent damage to cerebral tissue.[9,32,33] Injections of air into the carotid arterial system have produced variable results in the past, probably because in many cases the air failed to enter the cerebral circulation, as will be discussed later.

The experiments reported in this paper were designed to produce "arterial" cerebral emboli, limiting the gas injected to the cerebral circulation. The dog was used because the cranial circulation in this animal had been studied in detail by us.[10,11] Angiographic evidence was obtained of a method by which material injected into the internal carotid artery would pass to the brain, without shunting into the extracranial arteries through the multiple anastomoses between the intra- and extracranial circulations.[10]

The data obtained were examined for correlations between 4 variables—volume of air injected, intracranial pressure, morbidity, and mortality. Other gases were employed for comparison of their effects with those of air, and to determine the safety of some gaseous contrast media for ultimate clinical use.

Materials and Methods

Anesthetized with intravenous pentobarbital sodium (Nembutal) were 101 mongrel dogs of 15 to 20 kg. weight each. The dose was generally within the limit of 20 mg. per kilogram of body weight. The animals were divided into 4 groups, all subjected to the same general technique. Group I received different volumes of air foam, Group II a small amount of parenteral saline solution, Group III a slower injection of air foam, and Group IV received gases other than air.

Each animal was placed in the horizontal position on the left side and a PE-50 polyethylene catheter was inserted into the cisterna magna through a No. 19 thin-walled short lumbar puncture needle. The catheter was attached to a water manometer. The femoral artery was then catheterized with polyethylene tubing, and blood pressure recorded with a Grass Polygraph or a mercury manometer. Saline solution was flushed through the catheter in the femoral artery when necessary for clearing. Approximately 400 ml. were given during a 5-hour experimental period in the animals of Group I. Electrocardiograms were obtained in the first 30 animals, but not thereafter. Respirations were recorded in 20 dogs.

The head was rotated slightly to expose the ventral surface of the right side of the neck. A 6 cm. incision was made in the neck caudad from the angle of the mandible and parallel to the trachea. Dissection was continued until the carotid sinus and internal carotid artery were completely cleared.

A purse-string suture was placed in the adventitia of the common carotid artery and a Lindeman needle inserted into the lumen of the artery through the loop of the purse-string. The outer, nontraumatic part of the needle was then directed past the carotid sinus and into the internal carotid artery for a few millimeters. A PE-50 polyethylene catheter was threaded into the latter artery as far as possible, usually about 2 cm. The Lindeman needle was then withdrawn into the lumen of the common carotid artery. A small amount of saline solution was perfused slowly into the polyethylene catheter to prevent clotting.

Arterial blood, 8 ml., was drawn into a 20 ml. syringe containing a few drops of heparin solution, and the remainder of the syringe was filled with room air. The blood in the syringe was shaken forcibly for one minute. This time was chosen because bubbles then could not be made smaller by additional shaking. Any remaining air and large bubbles were eliminated from the syringe.

The desired amount of air-blood mixture (air foam) was transferred through a 2-way stopcock into a tuberculin syringe. The remaining space was filled with arterial blood. The air foam was then injected into the internal carotid artery in a time ranging from 4 to 8 seconds, because we considered this rate close to the physiologic flow rate.[10] This time included 2 to 4 seconds to inject the foam and 2 to 4 seconds to wash the bubbles out of the catheter with saline solution. Saline thereafter was slowly perfused for about 20 seconds to assure complete delivery of the air foam to the internal cerebral circulation. The position of the catheter inside the internal carotid artery

was again checked. The catheter was then withdrawn with the Lindeman needle and the purse-string suture tied to prevent bleeding.

Trypan blue was injected intravenously or intra-arterially in the femoral vessels 1½ to 2 hours after embolization. A 1% solution was used in a volume of 0.5 to 1 ml. per kilogram of body weight. The purpose of this injection was to aid localization of ischemic or infarcted zones by gross inspection.

Group II was composed of dogs treated in this same fashion, with the exception that these animals did not receive 400 ml. of saline solution in the femoral artery. Approximately 30 ml. were given to flush the carotid catheter.

The variation of the technique in Group III was that the injection of air foam was made slowly, in 8 to 16 rather than 4 to 8 seconds. Of the 10 animals in this group, 6 received the larger saline infusion of 400 ml. and 4 received 30 ml.

In Group IV, other gases were used as emboli by the technique described for Group I. These gases were oxygen, helium, nitrogen, and carbon dioxide, obtained from commercial cylinders labeled "pure gases." The volume of these gases ranged from 0.2 to 2 ml. of gas-blood mixture (gas foam).

Control dogs received 1 ml. of heparinized blood, but without air or gas foam by the technique used in Group I.

The animals remained 4 to 5 hours on the operating table, and then the wounds were closed. They received novobiocin and were observed daily.

Necropsy was done within 12 hours after death. Surviving animals were killed one week after the experiment, using pentobarbital by intravenous or intraperitoneal injection and subsequent exsanguination. All brains were examined, and gross and microscopic studies were performed. Whole coronal sections of the brain were embedded in celloidin and stained by the techniques of Nissl and Weil.

Interrelationships between the various recorded data were evaluated by calculating product-moment correlations coefficients. The clinical status was expressed quantitatively by arbitrary assignment of zero as a value for the normal dogs. Those animals with clinical signs or anatomic lesions which survived embolization were assigned a value of 1, and those dying as a result of the cerebral lesion were assigned 2. The "Student" *t*-test was used to examine the hypothesis that a correlation coefficient differed significantly from zero. Additional chi-square comparisons were used as contingency tests when necessary.[8]

Results

All animals were classified in 3 categories by the results of air embolization—normal, morbid, and fatal. The normal animals were those not presenting clinical symptoms or signs during the period of one week after the delivery of emboli, and which did not have macroscopic lesions in the brain. The morbid animals were those presenting clinical signs or anatomic findings. All fatalities occurred within 48 hours after embolization.

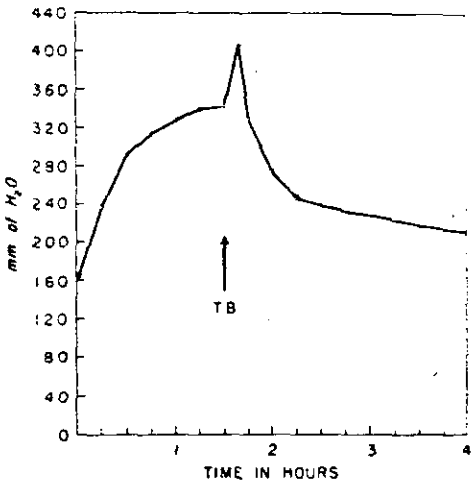

Fig. 1.—Composite diagram of the rise in cisternal pressure with injection of 0.6 ml. of air foam. These animals also received intra-arterial saline solution. Each point in the curve represents the mean cisternal pressure of 13 experiments. Air emboli were injected at zero time. The arrow indicates the time of injection of trypan blue.

A. *General Observations on the Effects of Air Emboli.*—1. Variations in Cisternal Pressure: Average initial pressure in all dogs was 147 mm. of water, with a range from 70 to 240. Control animals did not have significant pressure changes. Injection of air foam was followed by a sharp rise in cisternal pressure in most animals (Fig. 1). This rise began immediately after embolization, reaching a maximum between 30 and 90 minutes later, and thereafter the pressure came down slowly, but did not reach the original level at the end of 4 to 5 hours. Injection of trypan blue caused an additional, more transient rise in cisternal pressure (see Part A, 4).

Figure 2 represents the relation between ΔP (maximum increase or decrease) in cisternal pressure within 90 minutes of the time of embolization and the resulting status

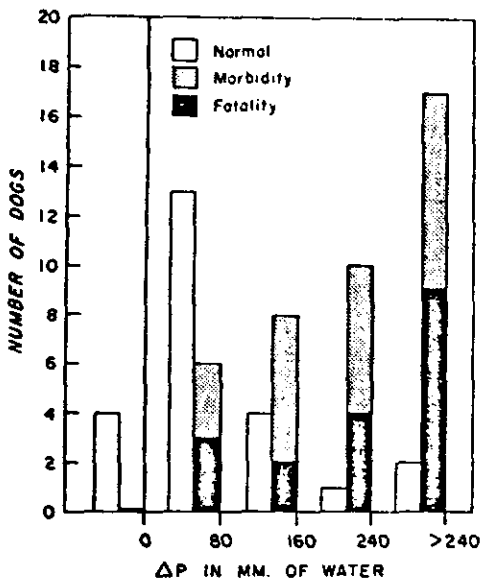

Fig. 2.—Histogram showing relation of changes in cisternal pressure to status resulting from air embolization in 66 dogs. ΔP is the maximum deviation from the initial pressure. Morbidity and mortality are well correlated with rise in cisternal pressure.

of 65 dogs in which pressure was measured after delivery of emboli, regardless of dose of air foam received. All 4 dogs with decreased pressure were normal. The proportion of normal animals was higher in those dogs with an increase in pressure below 80 mm., whereas the proportion of dogs with morbidity or death rapidly increased with higher cisternal pressures and was maximal when the rise was greater than 240 mm. The correlation between increase in pressure and resulting clinical status was a significant one ($r_{xy}=0.50$; $P<0.01$), although 3 of 30 dogs had an increase in pressure beyond 160 mm. of water and did not suffer morbidity or mortality (Fig. 2).

The average increase in pressure of all 24 dogs considered normal was 58 mm. (range, 35 to 280 mm.), regardless of dose of air received, whereas the average increase in pressure of 23 morbid dogs was 199 mm., and 205 mm. in the 12 experiments ending in fatality.

2. Variations in the Electrocardiogram (ECG): ECG's were taken on the first 30 animals, but recordings were subsequently discontinued because of lack of alterations. There were no recognizable changes in electrocardiograms during the 4 to 5 hours after embolization. The only animals with cardiac arrhythmias were those which suffered inadvertent puncture of the medulla oblongata or of vessels inside the spinal canal; 2 posterior fossa hematomas were found, and these animals were excluded from the series.

3. Variations in Blood Pressure and Respiration: A slight increase in blood pressure occurred in about one-third of animals immediately after embolization. This rise occurred when the carotid artery was handled at the time of withdrawal of the catheter and needle. In general, there was no other appreciable change in blood pressure during the experiments, with the exception of a sharp drop when trypan blue was injected. This fall lasted 1 to 3 minutes, and the range of fall of systolic pressure was 30 to 100 mm. of mercury. The beginning of this transient hypotension coincided with a sharp rise in cisternal pressure (Fig. 1). When a sharp elevation of blood pressure occurred during the procedure, an intra- or extramedullary hemorrhage was always present. Cardiac arrhythmias also occurred in these animals.

Immediately after embolization some dogs had a deep inspiration followed by slow, deep respiratory movements, but this effect was rare, and, in general, definite respiratory changes were not encountered.

4. Effects of Trypan Blue: Immediately after injection of trypan blue into the femoral vein or artery the cisternal pressure rose sharply, but it fell to the original level in 10 to 15 minutes (Fig. 1), with a simultaneous but more transient fall in blood pressure (see Part 3, above).

5. Clinical Observations: The animals dying as a result of embolization did so within 48 hours after injection of air foam. The survivors were killed one week after injection of emboli; many had clinical or anatomic signs of brain damage, designated as "morbidity." The 4 most significant clinical features were visual and motor defects,

involuntary movements and general behavioral changes. The visual defects gave the impression of blindness of the left eye. Retinal fibers are mostly crossed in the dog: hence, a right occipital lobe infarct produced almost complete blindness in the opposite eye, with absent or delayed lid closure when a threatening gesture was made. The dogs stumbled over objects placed on the left side of their path, and tended to walk in circles toward the unimpaired side.

Motor defects ranged from mild hemiparesis to complete hemiplegia. Weakness was often, but not necessarily, associated with blindness.

Involuntary movements were not present in dogs in the first 4 to 5 hours, and only 3 dogs had twitching of the contralateral extremities suggestive of convulsions in the postoperative period.

Behavioral changes occurred in some animals which appeared depressed or frightened. These observations throughout the postoperative period, although difficult to assess, were found by experience to be correlated with the presence of small cerebral infarcts.

6. Anatomic Findings: Macroscopically infarcted zones occurred mainly in the parieto-occipital distribution of the middle cerebral artery on the injected side. The territory of the ipsilateral anterior cerebral artery was malacic in a few cases. The contralateral hemisphere was grossly damaged in only one case in the anterior cerebral artery distribution, but microscopic infarcts were frequently found. The middle cerebral territory on the contralateral side was rarely affected, either grossly or microscopically.

Histologically, the infarcts were ischemic, only one being hemorrhagic. Infarcted zones were not found macroscopically in animals dying as a result of embolization within 48 hours after injection of air foam. In these cases, the small blood vessels were dilated, the brains were generally swollen, and the pyriform or cingulate gyri were herniated.

Microscopic examination revealed 2 types of damage. One type occurred in acute cases (dogs dying within 48 hours after embolization), and the other in chronic cases (animals killed one week after embolization). The acute changes consisted of focal zones of "blanching" of neurons or white matter, with some swelling of the perivascular spaces and minimal perivascular infiltration by small, round cells. The infarcted zones in the brains of dogs chronically afflicted showed a typical pattern composed of liquefactive necrosis and hyperplasia of surrounding blood vessels. Liquefactive necrosis was accompanied by large numbers of phagocytes. Hyperplasia was seen in focal zones of neuronal degeneration or cell loss, and was more striking in gray than in white matter.

Many animals considered clinically and macroscopically normal had histologic evidence of small embolic infarcts undetected by the more gross methods of clinical and macroscopic observation. Histologically, there was no apparent difference between infarcts caused by air and those caused by any of the other gases used.

B. *Effects of Modifications of Experimental Conditions.*—The volume of air foam injected was varied in the 45 animals in Group I (Table 1). All dogs in this group received approximately 400 ml. of isotonic saline solution during the experiment. A larger volume of air foam generally resulted in increased morbidity and mortality (r_{xy}= 0.41; $P<0.05$). Increasing the volume of air foam also tended to increase the cisternal pressure, but the correlation coefficient was considerably smaller ($r_{xy}=0.26$; $2>P>0.1$). The most useful predictor of the clinical outcome of embolization therefore is provided by the change in cisternal pressure rather than by the volume of air foam injected.

Dogs in Group II (Table 1) received 0.5 or 0.6 ml. of air foam in the internal carotid artery, but isotonic saline infusion was reduced from 400 ml. in Group I to approximately 30 ml. The latter amount was given to wash air foam through the system and to prevent clotting in the carotid artery tubing. The time of injection of air foam, as in Group I, was 4 to 8 seconds.

TABLE 1.—*Results Obtained by Changing Volume of Air Emboli (Group I), Altering Amount of Saline Given (Group II), and Slowing Speed of Injection of Air Emboli (Group III)*

	Vol. Air Foam Injected (Ml.)	No. Dogs	Speed of Injection (Sec.)	Isotonic Saline Administered (Ml.)	Morbidity Dogs	Mortality Dogs	Mean Increase in Pressure (Mm.)
Group I	0	2	4-8	400	0	0	—12
	0.2	5	"	"	1	0	57
	0.4	10	"	"	4	2	156
	0.45	4	"	"	2	0	261
	0.5	10	"	"	1	6	155
	0.6	14	"	"	3	7	190
Group II	0.5	10	"	30	5	1	117
	0.6	11	"	30	4	5	195
Group III	0.5	10	8-16	400	5	0	100

A significant difference between Groups I and II was noted in results obtained with 0.5 ml. injections. The mortality in Group I was 60%, but in Group II mortality was only 10%, and the mean increase in pressure (Table 1) was lower in the second group. With 0.6 ml. doses, the mortality was not significantly different in the 2 groups, and the mean pressure increase remained at the same level as in Group I. When the 0.5 and 0.6 ml. groups were combined, the final results obtained with embolization were not significantly different with or without saline infusion.

The dogs in Group III received 0.5 ml. of air foam in the same manner as in Groups I and II, but injection in the carotid artery was done at a slower rate (8 to 16 seconds). Of these animals, 6 dogs received the usual 400 ml. saline infusion and 4 dogs did not. The results were similar, regardless of saline infusion, and the findings in Table 1 (Group III) are therefore presented together. Mortality was nil in this entire group, and morbidity remained slightly lower than in Groups I and II. Mean increase in pressure was definitely lower than in the other groups.

The effect of 4 other gases—oxygen, carbon dioxide, nitrogen, and helium—was studied in Group IV (Table 2). The technique employed was the same as in Group I. Morbidity and mortality are shown in Table 2. Other data are not presented because of the small numbers of animals used with each gas. Oxygen was tolerated without mortality, but all these dogs had clinical or anatomic evidence of infarction. Carbon dioxide was well tolerated in doses up to 1.5 ml., but morbidity and mortality occurred with 2 ml. Nitrogen and helium foam produced effects similar to those of air foam, and morbidity and mortality results were comparable to the results obtained with air embolization.

Comment

These experiments demonstrate conclusively that, despite older reports,[13,29,32,35] amounts of air less than 1 ml. can be damaging or fatal when introduced into the arteries of the canine brain. In a more recent report, Fries et al.[15] found that a relatively large amount of air or gas was necessary to obtain mortality in dogs; there was no definite correlation between increasing doses and damage to the nervous system.

TABLE 2.—*Group IV: Effects of Oxygen, Carbon Dioxide, Nitrogen, and Helium Emboli*

Gas	No. Dogs	Dose (Ml.)	Morbidity	Mortality
O_2	3	0.5	2	0
O_2	2	1	2	0
O_2	2	1.5	2	0
CO_2	2	1	0	0
CO_2	2	1.5	0	0
CO_2	3	2	1	1
N_2	2	0.2	1	0
N_2	3	0.5	2	1
He	3	0.5	2	1
He	3	1	1	1

The dog has extensive interconnections of blood vessels between intra- and extracranial circulations, shown to be functionally effective by angiography.[19] Failure to damage the brain by air emboli, or the need for large amounts of intracarotid air to produce cerebral lesions, is in part related to escape of injected air emboli into the extracranial arteries. As little as 0.2 ml. of air foam in our experiments was capable of causing cerebral damage. We have shown in a previous paper [10] that clamping the ipsilateral common or external carotid artery promotes filling of the extracranial arterial system. Many investigators have attempted to fill the internal carotid artery and thence the brain by clamping the external carotid, but were unaware that the material so injected promptly flows into the distal part of the external carotid system. We have also shown that too rapid a rate of injection with large volumes of material also promotes extracranial filling. The technique described in this report requires that the catheter be placed in the internal carotid artery, that the rate of injection correspond to the physiologic rate of blood flow, and that clamping not be done on any artery. The emboli then have a high probability of reaching the brain without being shunted toward the extracranial circulation through the numerous collateral channels.

Air foam was used in these experiments rather than a single large bubble because air injected into an artery breaks into smaller bubbles of unknown sizes.[32,34] It was also thought that air foam more closely reproduced the conditions occurring when a bubble oxygenator is used in the procedure of bypassing the heart with an artificial lung. Because the air bubbles were in a foam, the actual amount of air injected was somewhat smaller than the dose reported herein, a thin film of blood surrounding each of the tiny bubbles.

A striking feature of the effects of air emboli upon the brain is the rise in intracranial pressure, reflected in the cisternal pressure (Fig. 1). The rise in pressure of cerebrospinal fluid and the volume of air foam were correlated with morbidity and mortality, but the pressure was the better predictor of the ultimate clinical status. It should be noted, however, that the gradation of dose was extremely small because the initial experiments were designed to determine the LD_{50} of air foam.

The experiments reveal some of the reasons for the variability of responses to air emboli. A slower injection of air foam may allow more absorption of air by the surrounding blood, and more time for air to pass through cerebral capillaries. Differences in individual animals in the rate of absorption of air, or in cerebral blood flow, also may influence the results. Undoubtedly, variations in the cranial blood vessels and the possible escape of small amounts of air foam into the extracranial system probably contribute to a lesser correlation of responses with the size of the injected dose. Air foam entering the cerebral vessels causes increased intracranial pressure, infarction, clinical signs, and mortality, but escaping air alters the dose in an unknown fashion.

We attempted to relate the rise in cisternal pressure to the initial pressure or the weight of the dog. Scatter diagrams failed to reveal any relation between these variables; hence, correlation coefficients were not computed. It is concluded that little if any of the observed changes in pressure are explained on the basis of initial cisternal pressure or weight.

The effect of infusion of 400 ml. of saline during the experiment was variable, depending on the dose of air foam. The mortality was higher in animals receiving 0.5 ml. of air foam and a large saline infusion than in those receiving the same amount of air foam and a small saline injection. The mortality was similar, however, in the 2 groups receiving 0.6 ml. Animals in Group III, with a slow speed of injection of air foam, had no difference in effects, regardless of whether large amounts of saline solution were given. The mortality in this group was nil.

A striking contrast was noted between the effects of air emboli and similar doses of

solid emboli. Babcock and Netsky [1] reported significant effects on respiration and thereafter on blood pressure and pulse rate as a result of cerebral embolization with celloidin emboli in volumes of 0.3 to 0.8 ml. Death was caused by respiratory inhibition and occurred within a few minutes. When air emboli are used death results in 2 days, and the mechanism is probably by increased intracranial pressure. Villaret and Cachera [33] described vasoconstriction in pial vessels when solid emboli were used, but never with air emboli. These workers showed that gaseous emboli may be held in smaller vessels for only 1 to 2 minutes and then pass beyond the capillaries. Another important factor is that solid emboli cause permanent blockage of blood vessels and hence may more readily result in embolism of the brain stem by overflow into the territory of the basilar artery. In recent unpublished experiments we have found that 3 ml. or more of air foam may result in changes of respiration, blood pressure, and electrocardiogram. The differences in systemic responses to solid versus gaseous emboli, therefore, are dependent on many factors—dosage, speed of injection, vasoconstriction, rate of passage through capillaries, and medullary effects.

The histologic differences are also of interest. Infarcts caused by solid emboli are most often hemorrhagic, although portions may be ischemic.[27] The infarcts produced by air emboli were almost entirely ischemic. These findings are in accord with those noted in human beings. When a patient with air emboli dies in a few minutes, abnormalities are not detected. Neuberger [26] described a patient who died 55 hours after embolism. The brain contained ischemic zones of cell loss. A patient with longer survival was described by Lhermitte and Barrelet,[21] who also found ischemic infarction. The reason for the absence of hemorrhage is not known, but the passage of air through capillaries into veins, and hence lesser damage to endothelial walls, may be an important factor. Fazio and Sacchi [14] obtained red infarcts with air emboli only if embolism was followed in 30 minutes by an intravenous injection of adrenalin, but not if the adrenalin was given at the time of embolism.

The clinical manifestations of arterial air embolism in man have been cited by Durant et al.[13] These symptoms include disorientation or coma, convulsions, hemiplegia, monoplegia, hemianesthesia, and hemianopsia. Slowing of the respiratory rate and Cheyne-Stokes breathing are the usual respiratory changes in man. Many of these signs were encountered in our experiments, but were modified by anesthesia or were not detected because of limitations of the neurologic examination in the dog. Respiratory disturbances were not noted under the conditions of our experiments when amounts of air foam less than 0.7 ml. were used. Respiratory inhibition, however, has been obtained with larger volumes of air foam (unpublished experiments). We believe both the larger dose and the escape of emboli to the medulla oblongata are factors in the causation of respiratory and cardiovascular changes.

Comparison of different gases was made both to determine the specificity of the effects of air emboli and because of the possibilities of using some gases intravenously as contrast media. Carbon dioxide was better tolerated than any other gas injected into the cerebral arterial tree. Nevertheless, small doses resulted in cerebral damage or clinical signs, and sufficiently large doses (2 ml.) were sometimes lethal. Oxygen failed to cause mortality in doses up to 1.5 ml., but the morbidity rate was high. Helium and nitrogen were comparable to air emboli in their detrimental effects. Further studies on a larger series are planned.

The toxic effect of trypan blue is of interest. This dye is widely used for studies of "blood-brain barrier," and for localization of cerebral lesions. Broman in his initial report [6] said little of the toxicity of the dye, but in a more recent paper [7] indicated that rapid intravenous injection in guinea pigs induces fatal respiratory suppression, and

that in high concentrations the dye has a toxic effect on the blood-brain barrier. The injection of trypan blue always caused a rise in cisternal pressure and probably contributed to the mortality in our experiments. The dye must be considered toxic. The mechanism of its toxicity, though, is unknown to us, and will be the object of further study.

Summary and Conclusions

A new method is described for the production of air embolism of the cerebral arteries in the dog; the escape of air from the intra- to the extracranial circulation is reduced to a minimum. The method is simple and reliable, and was used in a study of 101 dogs. Amounts of air foam as small as 0.4 ml. may result in death. Air embolism of the cerebral arteries causes a prompt rise in intracranial pressure and then focal cerebral infarction. The subsequent neurologic signs in the dog are similar to those described in man. The clinical effects of air embolism are best correlated with the accompanying rise in cisternal pressure. Death occurs within 48 hours from increased intracranial pressure. Respiratory inhibition and electrocardiographic changes are nil with the doses of air emboli reported in this paper.

The effects of air emboli are greater with increasing doses, although some variation in results is obtained; the reasons for this are discussed. Saline infusion of 400 ml. during the experiment has little effect on the results. A slow rate of injection of air emboli causes less damage than does injection at the physiologic rate of flow.

Infarction produced by air emboli is ischemic; in contrast, solid emboli often lead to hemorrhagic infarction. The physiologic and anatomic effects are generally less with air than with solid emboli, in part because air bubbles can enter the venous system by passing through the capillaries, and because air is less damaging to blood vessels.

Carbon dioxide is the least harmful of the gases studied, but it can produce cerebral damage or death when given in 2 ml. doses. Oxygen is intermediate in its effects. Nitrogen and helium emboli are comparable to air in damaging the brain.

Trypan blue is toxic, causing a transient increase in intracranial pressure and a fall in systemic blood pressure.

We are indebted to Dr. H. O. Goodman for statistical evaluations and helpful suggestions. Mr. Laurie Moore assisted us in many of the experiments.

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W O R K S H O P

on

ARTERIAL AIR EMBOLISM

AND

ACUTE STROKE

held on

Friday, 13 May, 1977
Toronto, Canada
(preceding the UMS Annual Scientific Meeting)

John M. Hallenbeck
Leon J. Greenbaum, Jr.
Chairmen and Editors

This workshop was supported by the National Institute of Neurological Diseases and Stroke and by the Office of Naval Research.

The publication of the workshop report was supported by the National Library of Medicine, National Institutes of Health, Public Health Service, Department of Health, Education and Welfare.

CARDIOVASCULAR EFFECTS OF ARTERIAL AIR EMBOLISM

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Bethesda, Maryland

Case reports of air embolism associated with submarine escape training have appeared in the diving literature since 1930 (26). Early reports described symptoms ranging in severity from mild neurological disturbances to unconsciousness, cardiovascular collapse and death (15,24). Fatal symptoms in the last instance were usually observed as soon as the diver had surfaced. Although the phenomenon was first thought to result from increased intrathoracic pressure (Valsalva phenomenon) (20), in 1932 Behnke (1) and Polak and Adams (25) determined the cause to be rupture of the alveoli with subsequent entrance of air into the circulation.

Air embolism is also encountered in the clinical setting as a result of various diagnostic and surgical procedures. Although infrequent, these cases are of concern because they often lead to serious permanent injury or death (14).

While it is reasonable to assume that the neurological symptoms encountered in air embolism result from the presence of air in cerebral blood vessels interfering with perfusion of neural tissue, the cause of the cardiovascular symptoms is far from clear. The cardiovascular symptoms following arterial air embolism could result from three or possibly more mechanisms acting alone or in combination with each other.

First, air entering the coronary arteries could lead to myocardial infarction with resulting arrhythmias and ischemic damage to the myocardium. These events could of course cause immediate death. Second, a bolus of air in the ventricle itself could produce an air lock and interfere with cardiac pumping action. Third, air entering the cerebral circulation could initiate hyperactivity of the autonomic nervous system resulting in changes in blood pressure, cardiac arrhythmias and even ventricular fibrillation and death. Cerebral air embolism

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Naval Medical Research and Development Command, Research Task No. M0099.PN001.1155. The opinions and assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large. The experiments reported herein were conducted according to the principles set forth in the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Resources, National Research Council, DHEW, Pub. No. (NIH) 74-23.

can also cause apnea or other respiratory problems which could worsen the cardiovascular picture.

In reviewing the literature, there is experimental evidence that at least two of these factors are involved in the cardiovascular response to air embolism. With regard to the first two mechanisms, Geoghegan and Lamb (9), using the dog as the experimental animal, found that air reaching the left heart is capable of causing almost instant death by filling the coronary arteries, but that air in the cavity of the ventricle does not impair the function of the heart.

With regard to the indirect or neural mechanisms, de la Torre et al. (3) studied the cardiovascular and respiratory effects of cerebral air embolism in the dog after separating the anterior and posterior cerebral circulations by applying clips to various points on the Circle of Willis. They found that air restricted to the posterior cerebral circulation caused severe respiratory and cardiovascular effects including acute hypertension, ventricular fibrillation and death. Conversely, air restricted to the anterior cerebral circulation caused no cardiovascular effects. De la Torre and colleagues concluded from these studies that damage to the brain stem alone was responsible for the cardiovascular response to cerebral air embolism. This work was confirmed in 1971 by Simms et al. (27) who found that introduction of small amounts of air into the vertebral arteries of dogs caused severe cardiac arrhythmias.

There is additional evidence that these indirect or neural mechanisms may be especially important in diving accidents. For example, Van Allen et al. (29) found in the dog that distribution of air introduced into the pulmonary vein was determined by body position. In the horizontal or head-down position, air was distributed mainly to the coronary arteries and other peripheral structures, while little air was found in the cerebral vessels. However, in the vertical or head-up position, air was distributed mainly to the cerebral vessels, with little air found in the coronary arteries. Since divers are almost always in the upright position at the time of air embolism, it is probable that air readily enters the cerebral vessels and that cardiac dysfunction may result indirectly from neural mechanisms.

It is pertinent at this point to review what is known about the nature of the neural mechanisms involved in cardiovascular dysfunction and what is known about the role of the nervous system in cardiac arrhythmias encountered clinically. It has, of course, long been known that hyperactivity of the autonomic nervous system can lead to alterations in blood pressure and disturbances in cardiac rhythm. It has been demonstrated that either sympathetic or parasympathetic stimulation alone can cause cardiac arrhythmias (8,13) and that simultaneous activation of both systems most readily causes arrythmias (21). In fact, it has been shown that almost every type of clinically occurring cardiac arrhythmia can be experimentally induced

by stimulation of some part of the autonomic nervous system (22). In recent years there has been increasing interest in the role of the autonomic nervous system in the generation and treatment of cardiac arrhythmias. Although arrhythmias have in the past been thought to occur because of disturbances in impulse formation or conduction within the heart, there is a growing body of evidence that neural influences may be equally important (17). A number of studies have demonstrated a significant involvement of the nervous system in various types of cardiac arrhythmias, including those accompanying digitalis toxicity and myocardial infarction (2,10,11,12,18). For example, stimulation of the sympathetic nervous system has been found to facilitate the development of arrhythmias following digitalis administration (7) or coronary occlusion (19), whereas interruption of sympathetic neural activity has been shown to exert a protective effect (10,23,31). There is also clinical and experimental evidence that arrhythmias and other cardiovascular problems can occur following head injury (6), spinal cord injury (4), and intracranial hemorrhage and stroke (16,28,30). In the latter case, cardiovascular events can include myocardial damage, cardiac arrhythmias and sudden death (5). Since these effects are presumably the result of cerebral ischemia, and since the damage of air embolism is also presumably one of ischemia, one might expect the phenomena accompanying cerebral air embolism to be similar to those accompanying stroke.

In summary, there is considerable evidence that cardiovascular dysfunction can result from neural influences and that the autonomic nervous system is, in fact, involved in many types of arrhythmias and cardiovascular problems seen clinically. With regard to dysbaric air embolism, these studies indicate that whether air enters the coronary arteries or enters the cerebral circulation, neural factors may be involved in the resulting cardiovascular responses. These considerations suggested to us that a careful study should be made of both direct cardiac and indirect neural mechanisms involved in the acute cardiovascular problems of arterial air embolism. This approach is based on the premise that only through an understanding of the specific mechanism involved can a rational therapeutic regime be developed.

In designing our experiments we set out to address the following questions:

1. What are the specific cardiovascular responses to air embolism?
2. Are the cardiovascular changes the result of air in the heart and coronary arteries, or of autonomic nervous system activity induced by the presence of air in the cerebral circulation, or both?
3. Are neural effects mediated by sympathetic or parasympathetic pathways, or are both divisions of the autonomic nervous system involved?

4. Do hemodynamic and reflex changes associated with increased intrathoracic pressure and pulmonary barotrauma (which may occur during decompression with airway obstruction) alter the cardiovascular effects of air embolism alone?

We have only recently begun our studies, which at this time raise more questions than they provide answers. Nonetheless, we will describe our preliminary findings.

In the first series of experiments, cats anesthetized with chloralose were placed in a stereotaxic apparatus so that the head was in an upright position well above the level of the heart (resembling the posture of surfacing divers). Ventilation was controlled to maintain blood gases and pH within normal physiological limits. Continuous measurements were made of arterial blood pressure, heart rate, electrocardiogram, and left ventricular pressure and contractile force. Air was infused into the left ventricle via a cannula introduced through a brachial artery. Infusion of air was continuous at a rate of 3 cc/min until abnormalities appeared in the electrocardiogram, or until blood pressure began to fall precipitously.

Our results from seven such experiments are as follows: Two quite different kinds of response were observed after 3 to 8 cc of air had been injected. In 3 of 7 experiments, infusion of air resulted in an increase in heart rate and blood pressure and the occurrence of a variety of severe cardiac arrhythmias. These severe cardiovascular disturbances lasted for approximately 15 minutes, followed by a gradual return to a more normal cardiovascular status. All of these animals survived a one-hour observation period. In contrast, 4 of the 7 animals exhibited few cardiac arrhythmias but developed an immediate depression of arterial blood pressure and left ventricular contractile force, which ended in death within 2-3 minutes. The electrocardiogram of these animals revealed a marked elevation of the S-T segment, suggesting coronary infarction.

Figures 1 and 2 illustrate one example of the response to air embolism characterized by arrhythmias and acute hypertension. In all figures there are 3 panels, each consisting of 4 traces. The top trace is the first derivative (dp/dt) of the left ventricular pressure curve, and is a measure of left ventricular contractile force. Beneath the dp/dt is the left ventricular pressure (LVP). Below it is the femoral arterial blood pressure (BP), and on the bottom is the electrocardiogram (ECG, Lead II). In Fig. 1, air was injected into the left ventricle, beginning at the arrow. One minute later, there were decreases in contractile force, left ventricular pressure and arterial blood pressure. Also at one minute, cardiac arrhythmias began to appear. At 2 minutes, contractile force and blood pressures were increased and the arrhythmias progressively worsened. Figure 2 shows a continuous recording for 36 seconds beginning 3 minutes after air

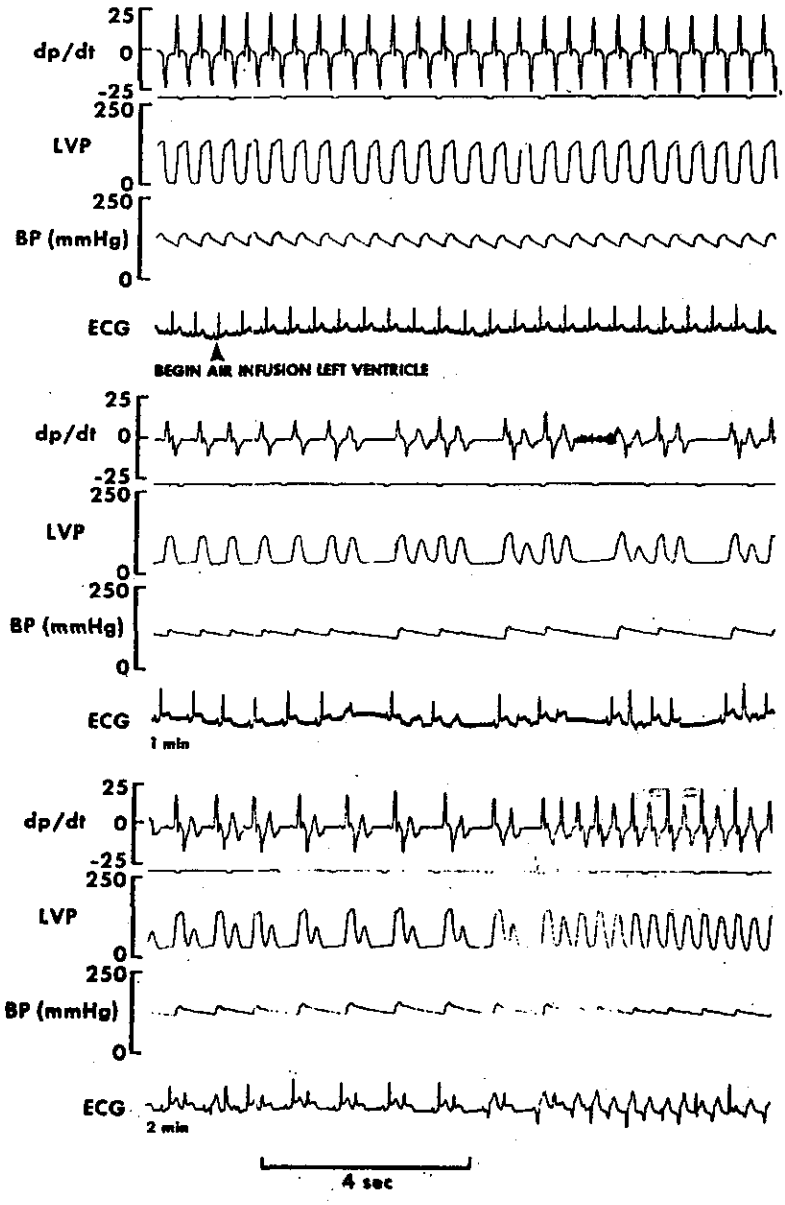
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Figure 1.

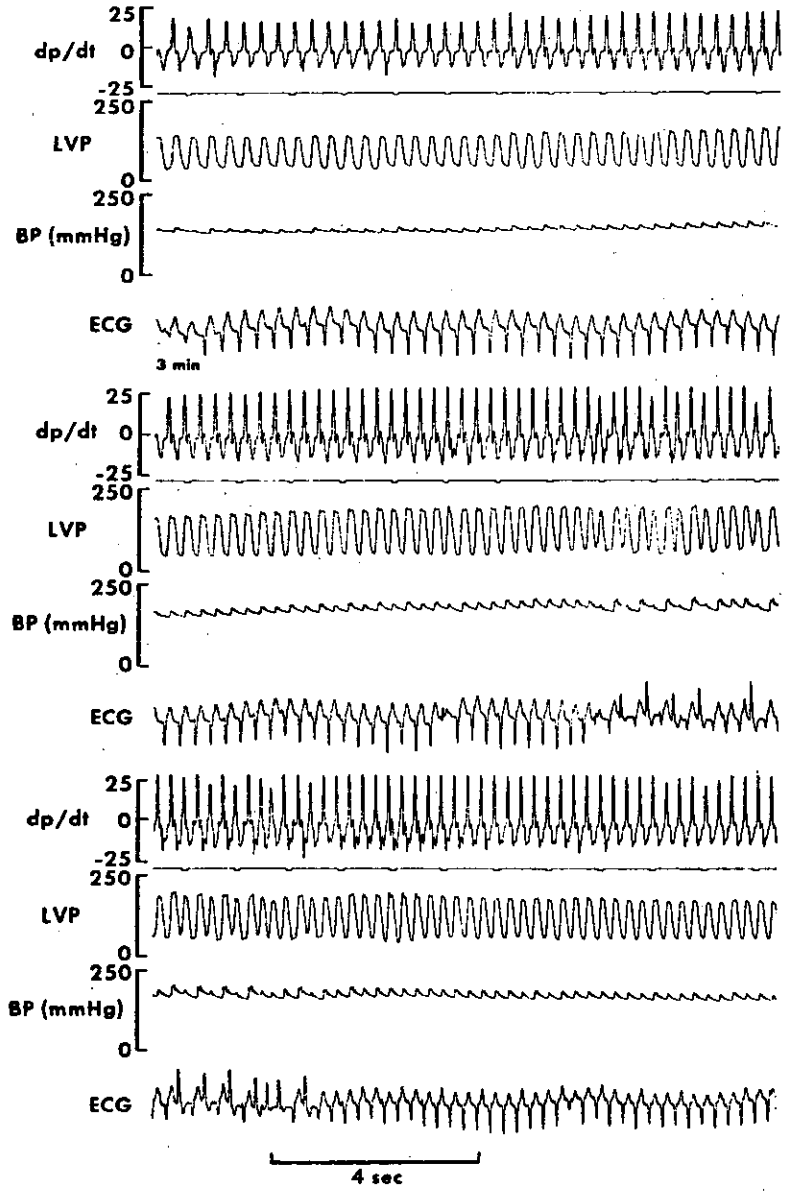
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Figure 2.

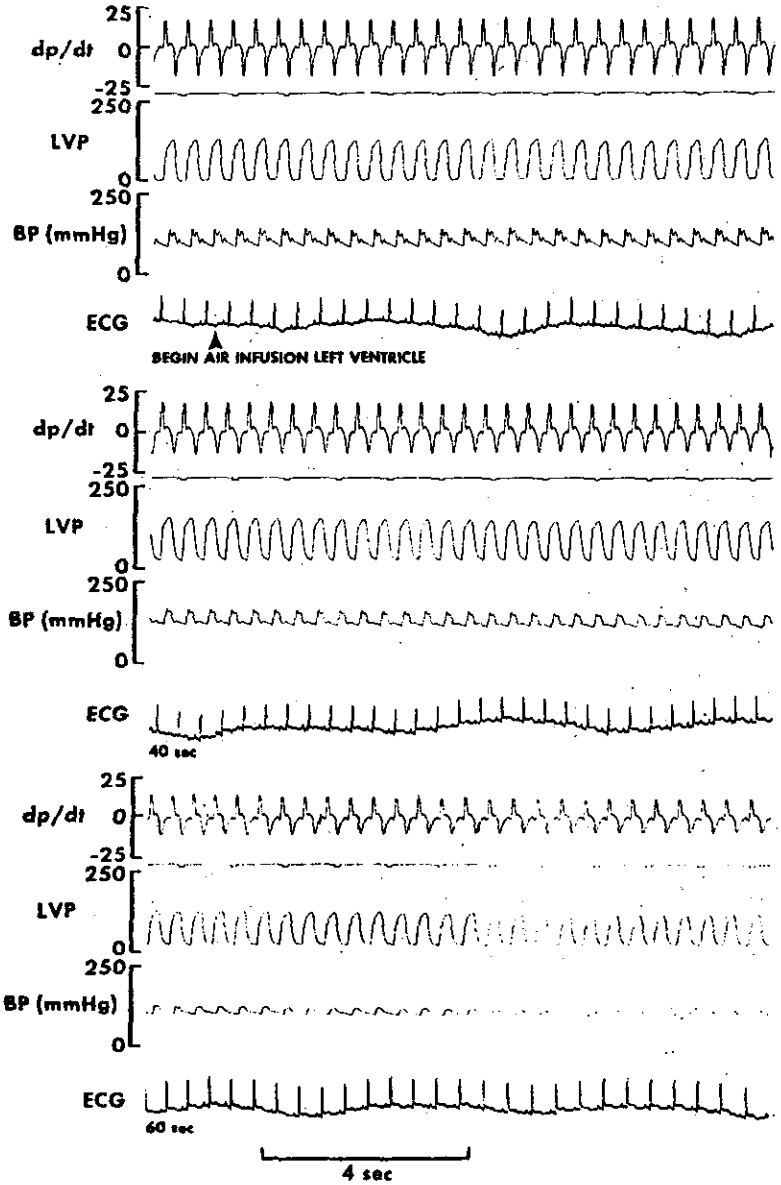
embolism. As can be seen, contractile force and blood pressures continued to increase and the ventricular tachycardia continued with some shifting of the pacemaker for brief periods. In this animal arrhythmias persisted for approximately 15 minutes, but the animal survived the one-hour observation period.

Figures 3 and 4 illustrate another experiment in which the response to air embolism was characterized by immediate hypotension and death. Figure 3 shows that for the first minute after the beginning of air infusion into the left ventricle there was little change in the cardiovascular status of the animal. Figure 4 shows that approximately 70 seconds after beginning air infusion, both blood pressures began a steady decrease which became pronounced at 100 seconds. Also, at 100 seconds the left ventricular contractile force was severely depressed, and at 120 seconds the animal was essentially dead. The electrocardiogram did show some S-T elevation at 70 seconds, but there were no ventricular arrhythmias seen up to the time of death.

To obtain further evidence for a neural mechanism in the genesis of the response characterized by arrhythmias and hypertension, we have performed a small number of experiments in which infusion of air has been made into arteries supplying the brain, thus excluding direct infusion of air into the coronary arteries. In three experiments, air was injected into the vicinity of the origin of the right vertebral artery through a catheter introduced through the brachial artery. All of these animals exhibited hypertension and arrhythmias and all survived the one-hour observation period. We observed similar results in two experiments after infusion of air into the internal carotid artery. One of these experiments is illustrated in Figs. 5 and 6. In Fig. 5, the arrow marks the beginning of air infusion into the cerebral circulation. At 40 seconds, blood pressures began to rise, and at 1 minute, arrhythmias began to occur. Figure 6 shows that at 2, 3, and 4 minutes, a continuous ventricular rhythm was accompanied by increased blood pressure and contractile force. In this animal, sinus rhythm and normal blood pressures returned approximately 10 minutes after the beginning of air infusion.

These preliminary observations suggest that the response to air embolism characterized by acute hypertension and severe arrhythmias is due to autonomic disturbances evoked by cerebral air embolism. Conversely, the response characterized by hypotension, left ventricular failure and death appears to be the result of coronary embolization. This tentative opinion is based on the observations that injection of air into the cerebral circulation produced the first type of response but not the second.

In continuing these experiments, we will use autonomic blocking drugs to separate further the direct cardiac effects from the indirect neural effects of air embolism. These experiments will also allow us to determine the specific autonomic mechanisms involved in the cardiovascular events observed. In later studies we will seek to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ECG
60 sec
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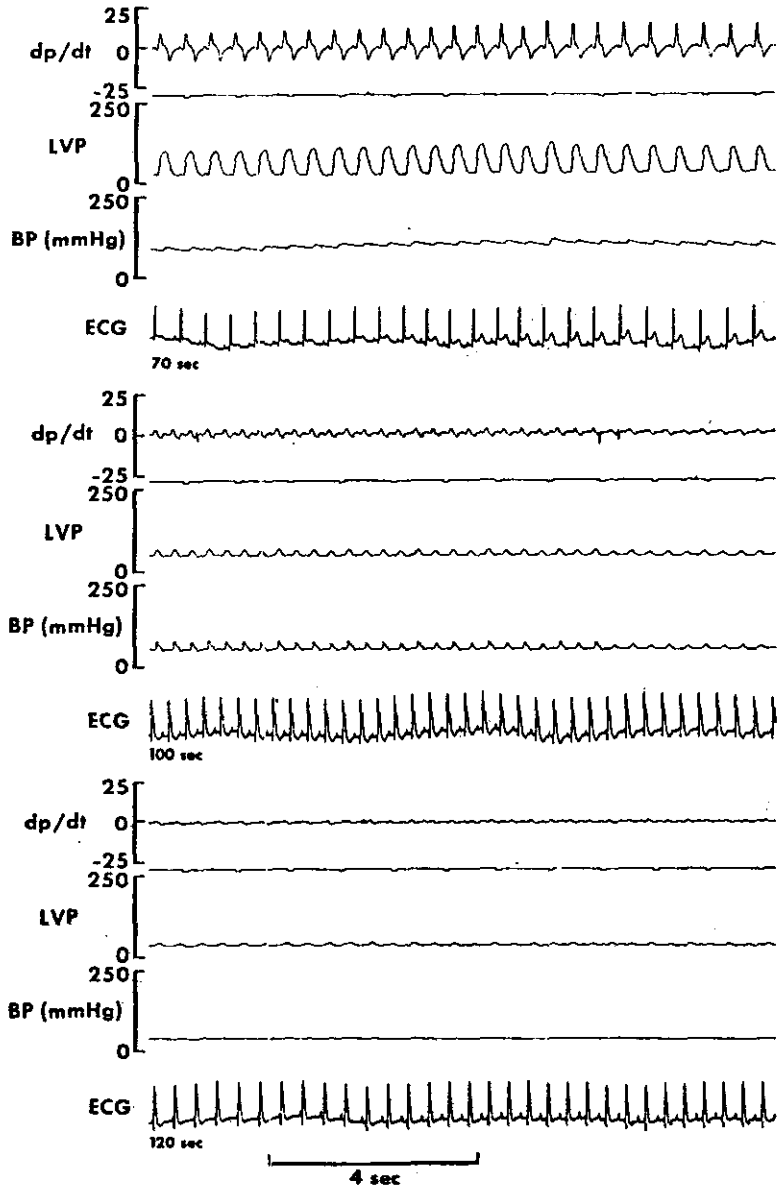
Figure 3.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ECG
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120 sec
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Figure 4.

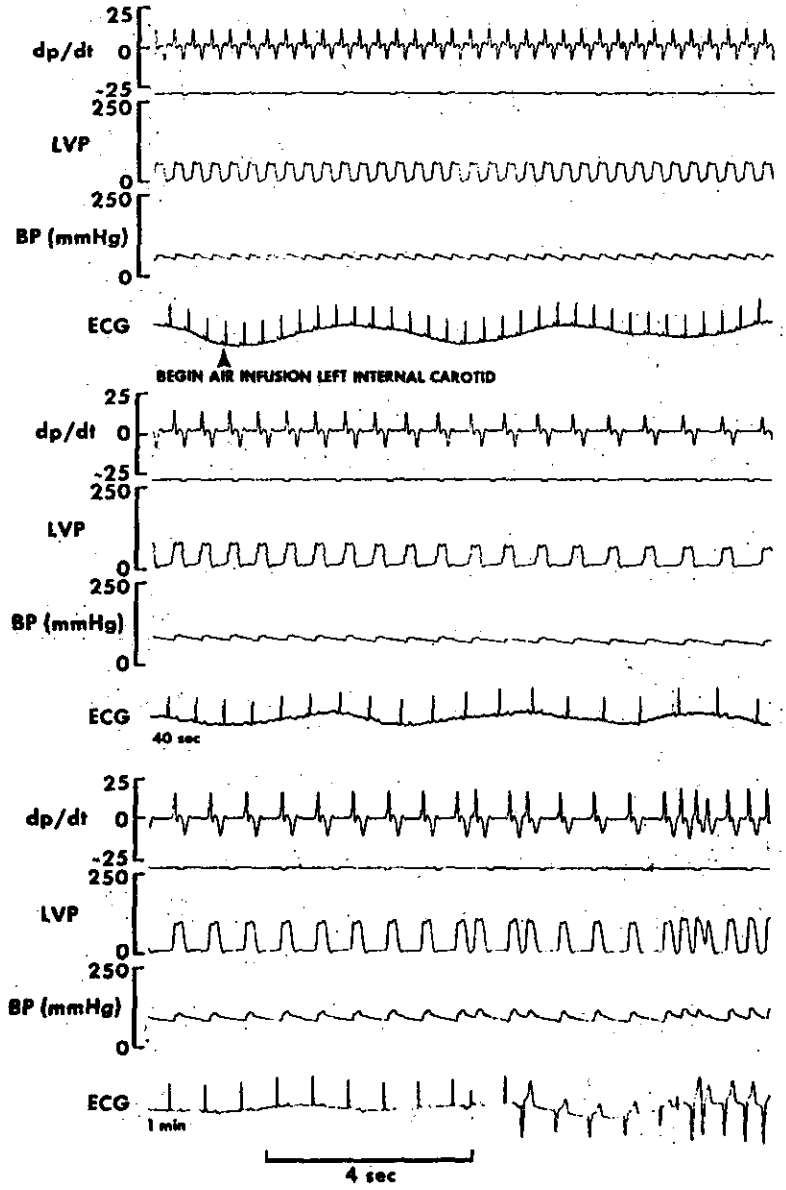
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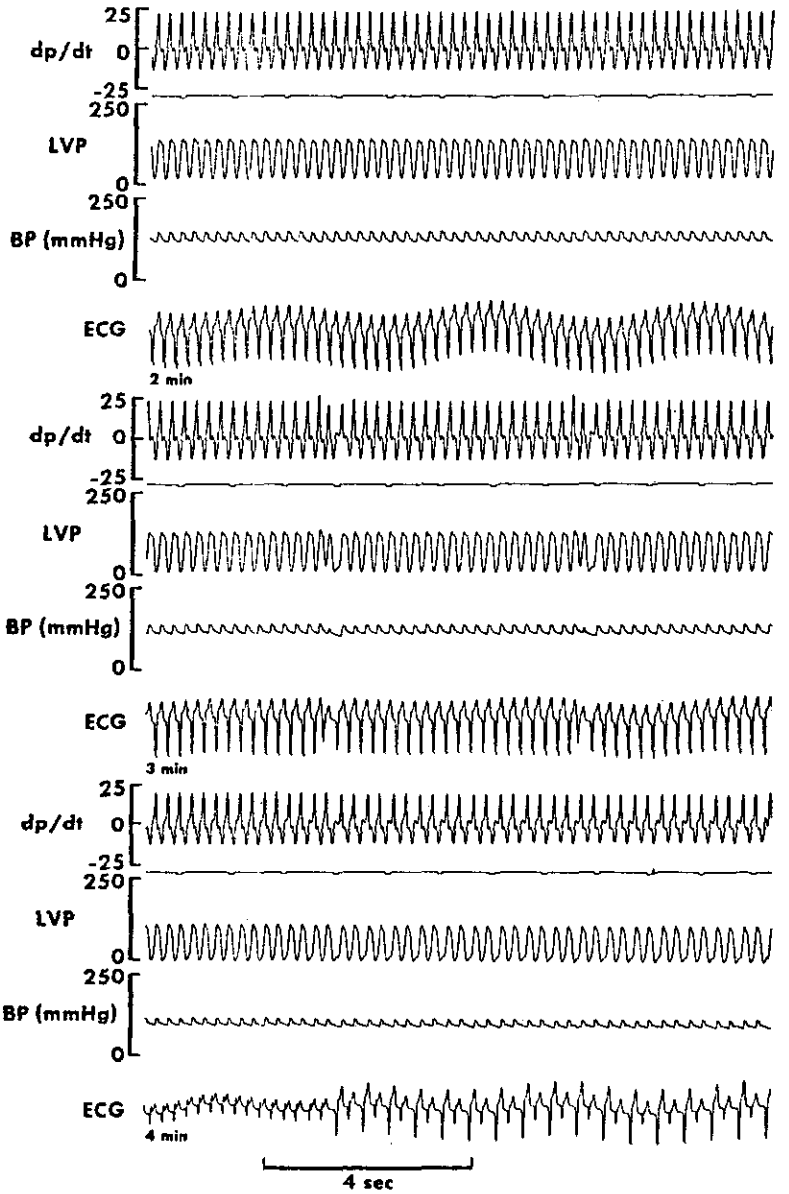
Figure 5.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BP (mmHg)
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ECG
4 min
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Figure 6.

determine whether the effects of increased intrathoracic pressure alter the cardiovascular response to air embolism alone. We will then perhaps have sufficient information to formulate and test new methods of treating the acute cardiovascular effects of dysbaric air embolism.

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AMTE(E) R 78-402

CAUSES OF DEATH IN SUBMARINE ESCAPE TRAINING CASUALTIES: ANALYSIS OF CASES AND REVIEW OF THE LITERATURE

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July 1978

ABSTRACT

Arterial gas embolism can sometimes cause sudden death despite immediate recompression. Two such fatalities have occurred at the Submarine Escape Training Tank, HMS DOLPHIN. Possible reasons for these treatment failures are considered. On the basis of indirect evidence and experiments reported in the literature, it is deduced that cardiac arrhythmia was the terminal event, and that the cause could be either embolisation of the coronary arteries or autonomic reflex originating in the embolised brain stem. Two specific additions to the therapeutic regimen are advocated. First, an electrical defibrillator should be developed which can be used safely in a wet recompression chamber at 50 msw pressure of air. Second, treatment with both atropine and propranolol may abolish reflex arrhythmias in refractory cases. In addition, hyperoxic breathing mixtures should be used during resuscitation at pressure. Recommendations for further research are discussed, and guidelines for the management of the pulseless gas embolism casualty are given.

INTRODUCTION

In 1974, the Submarine Escape Training Review Committee was convened to review all aspects of submarine escape training and make recommendations to guide future policy and development. In its final report (2), the Committee reaffirmed the desirability and the basic principles of submarine escape training (SET), but recommended certain modifications to procedures which might reduce further the small incidence of training accidents. The Committee also recommended that research be undertaken into pulmonary barotrauma, the commonest serious form of SET accident, including ways to improve the treatment of casualties.

The aim of this study was to analyse and evaluate SET arterial gas embolism casualties and to review pertinent literature, and thereby (a) to identify modifications of current practice which might prevent future treatment failures, and (b) to identify avenues of research which might provide new approaches to therapy. The etiology of pulmonary barotrauma is not the concern of this report, although it is acknowledged that the prevention of pulmonary barotrauma should be the ultimate goal of research. The measures discussed in this report will help to maximise the probability of complete recovery for the few trainees who are affected by arterial gas embolism.

BACKGROUND

The procedures and equipment for submarine escape training are described in articles by Crocker (9), Lambert (34), and Todd (62). During the development of SET techniques, arterial gas embolism caused by pulmonary barotrauma was identified as the most frequent cause of the serious illnesses which occasionally followed ascent. Descriptions of SET accidents and treatment procedures are given by Polak and Adams (50), Moses (48), Van Genderen (64), and Elliott et al (17). A clinical description of 79 cases of pulmonary barotrauma is given by Gillen (23).

By the time SET was begun at HMS DOLPHIN in 1954, arterial gas embolism was well recognised as an occupational hazard for the trainees. A chamber facility was

provided for recompression therapy at the top of the training tank. Any trainee having symptoms or signs of arterial embolism was immediately recompressed to 50 metres of seawater (msw) equivalent pressure (6 bars absolute) breathing air, usually arriving at the therapeutic depth within half a minute of the decision to treat being made. The subsequent decompression procedure has varied over the years depending on the response of the patient. In some cases, patients with minor symptoms, especially giddiness, were thought to be "false alarms", having recovered completely during compression. Some of them were decompressed on standard diving tables. Most have been decompressed on some form of therapeutic schedule specified in the RN Diving Manual of the time. The procedures generally resembled the current Tables 52, 53, 54 or 55 (52). In recent years, all patients have been decompressed, after two hours at 50 msw, on a special 38.5-hour schedule consisting of RN Table 55 to the end of the 18 msw stop, then Table 71 to the surface (52). The patient is always accompanied by at least one attendant, and is examined by a medical officer during the treatment. Critically ill patients are attended by the medical officer throughout the treatment.

From the commissioning of the SET Tank (SETT) at HMS DOLPHIN until March 1977, approximately 57,000 trainees have made about 212,000 ascents through the water. In that time, only 91 ascents have ended in incidents compatible with arterial gas embolism. This corresponds to an incidence of about 1/2300 ascents, or 1/630 trainees (not adjusted for repeaters).

I have made the presumptive diagnosis of arterial gas embolism in these 91 cases on the basis of a review of the narrative summaries of all 137 formally reported incidents at the SETT*. The group of embolism cases includes many whose symptoms were minor and relieved so quickly by recompression that the diagnosis might be considered doubtful. However, it is instructive to note that one third of those who were thought to be "false alarms" later suffered a relapse which confirmed the occurrence of arterial embolism. I have therefore categorised as arterial gas

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embolism any trainee for whom I would have advised recompression. The group includes patients with nearly any kind of neurologic or constitutional symptom (except pain alone) occurring within a few minutes of the ascent. Accidents which resulted from chamber runs or re-entry tower operation were excluded from the analysis, as was the one fatal accident which occurred to an instructor in the single escape tower.

Table I summarises the distribution of the major signs and symptoms which appeared during the initial phase of these 91 episodes. When more than one conspicuous manifestation was present, all were included; therefore the total adds to more than 100%.

Coma	35%	Collapse without coma	8%
Stupor	23%	Visual change	9%
Dizziness	15%	Mono- or hemiparesis	20%
		Focal sensory change	12%

TABLE I. Major signs and symptoms in 91 cases of arterial gas embolism.

The term coma includes patients with a period of unconsciousness, however short, with or without convulsions. Stupor includes those who were responsive to some degree but were confused, disoriented, or "not quite right". This group also includes a few with ataxia and athetosis. Dizziness includes both vertigo and faintness; it is usually not possible to distinguish the two in the records. Collapse refers to sudden loss of postural tone in patients who were said to be aware but usually unable to communicate. The presenting signs were rarely observed by the medical officer. In most cases, the patients were recompressed and largely relieved before any time could be taken for thorough evaluation. This is proper and in keeping with the philosophy that nothing should be allowed to delay treatment by recompression, but it means that the description of the initial episode can only be approximate. Gillen (23) has published descriptions of a few US Navy cases in which careful clinical observations were made.

The result of recompression treatment in arterial gas embolism as it occurs in SET is usually dramatic relief. Although there was evidence of recurrence or relapse in 33 of the 91 cases analysed, all but 9 were completely free of illness upon completion of the decompression. A further 5 returned to normal in 2 days to 2 months after surfacing. The four patients who died make the ultimate failure rate 4.4%. Two of them were completely relieved by the initial recompression but later died after sudden relapse and then a prolonged course of deteriorating cerebral function. The other two were apparently apnoeic and pulseless from the start and never responsed to therapy. Efforts to improve therapy, as recommended by the Submarine Escape Training Review Committee, must therefore be directed toward understanding the causes of these four treatment failures and preventing similar occurrences in the future.

ANALYSIS OF CASES

This analysis is based on an initial hypothesis that those who died immediately were the victims of some unique factor among the immediate consequences of gaseous emboli which prevented the normal salutary response to recompression. The delayed deaths, on the other hand, are thought to have suffered some different consequence, with a delayed but progressive effect on cerebral function. The factor likely to be responsible for this second group is vasogenic cerebral oedema, caused by vascular damage done by the initial contact with gaseous emboli (1, 6, 8, 32,38,51,67). An alternative suggestion is that a secondary change in the blood or the vessel prevents the restoration of microvascular flow despite the clearing of emboli - the "no-reflow" phenomenon (1, 29,30). Some of the non-fatal relapses may have been due to a second episode of pulmonary barotrauma during the therapeutic decompression, which then responded to repeat recompression. However, some of the relapses, including a fatal one, occurred prior to leaving 50 msw, and could not therefore be due to a recurrence of barotrauma. Modifications to treatment which are aimed at preventing vasogenic oedema or the no-reflow phenomenon would be a sound approach to eliminating delayed treatment

failure. Research is proceeding along these lines (1, 30).

The purpose of the remainder of this report is to discuss the first category of treatment failures - those who suffer immediate profound collapse and do not improve with recompression. The two SETT casualties concerned are summarised in the Appendix.

In the first case, the patient never recovered even though he was recompressed and artificially ventilated within a minute of the onset. Closed-chest cardiac massage was not begun until 5 minutes had elapsed, although it seems that cardiac arrest had occurred initially. This delay of 5 minutes and the lack of any drug treatment other than epinephrine are sufficient explanation for the failure to recover. However the exact nature of the cardiac arrhythmia is unknown, since it was not possible at the time to do electrocardiography in the recompression chamber.

The second patient showed opisthotonos and agonal respirations which suggest that cardiac arrest may have occurred a short time after the onset. Although cardiac massage and artificial ventilation were given immediately, the supplemental therapy was less than optimal. Again, ECG diagnosis was not available at the time.

The post mortem findings in either case are not helpful. Since death occurred at pressure, prior to decompression, the presence of bubbles in the coronary arteries or in specific areas of the brain is not diagnostic. Indeed, Smith-Sivertsen (57) has shown that dead animals can absorb enough inert gas at pressure to cause bubble formation during decompression, even if they were dead before compression.

In addition to the two cases summarised, there were 21 other patients who presented with sudden profound collapse and unconsciousness, and at least 4 of them were briefly apnoeic. Whether any of them suffered a survivable form of cardiac arrhythmia cannot be determined. Only four of them had ECG done

after recovery, and those were entirely normal.

In the US Navy SET programme, covering 49 years, the treatment failures can be divided into the same two categories (48,64). Of eight deaths, five have had sudden apparent cardiorespiratory arrest. Four were unresponsive to therapy, and one, occurring at sea in early trials, was not recompressed. All of these cases also had bubbles in their coronary arteries (48), but only the one who was not recompressed is free of the ambiguity of post-decompression bubbles. ECG diagnosis was not available in these cases, either.

It is central to this study to consider what unique factor could apply to the sudden death victims which would explain their failure to benefit from recompression. Several possibilities must be mentioned. First, if the critical embolic event directly or indirectly caused cardiac arrest, then recompression alone could not clear the circulation of gas unless action were taken to re-start the heart. In the cases cited, not all the constituents of optimal cardiopulmonary resuscitation were available or used. In particular, electrical defibrillation cannot be done safely in the SETT recompression chamber.

Second, although there is no way to ascertain the dose of air which caused the accidents, it is conceivable that a particularly massive injection of air could either obstruct ventricular pumping action or exceed the capacity of the vascular system to clear it.

Third, untreated apnoea would ultimately result in cardiac arrest, but both of the RN casualties received adequate expired air ventilation without delay.

Fourth, if vessels became thrombosed during the circulatory arrest, then recompression would not be expected to restore flow. However, in the sudden death cases, the time course was too short for this explanation without pre-existing vascular disease.

Finally, massive pneumothorax could interfere with ventilation, or massive pneumomediastinum or pneumopericardium could obstruct venous return or ventricular filling. However, these could be at least temporarily relieved by recompression to 6 bars absolute.

Thus only the first two of these five possibilities seem viable. Of these, the second is the less hopeful. The implication could be that the therapeutic depth should be increased, but to have a significant effect by Boyle's law, the depth would need to be increased to depths at which serious practical difficulties become limiting. Post mortem findings in the RN cases do not support the contention that the quantity of gas present in the circulation was in any way unusual. Animal experiments reported by Geoghegan and Lam (22) showed that the presence of a large amount of air in the ventricles did not cause death by "air lock". Only the arterial emboli were responsible. As for the optimal depth of recompression, no systematic, dose-response study has been reported which would define the probability of benefit from recompression beyond 50 msw. Published animal experiments do show that the directly observable effect on bubble size is greatest in the first 10 to 30 msw of pressure (27,65). Waite and co-authors observed the cortical circulation directly in embolised dogs during recompression. They saw no case in which all traces of vascular bubbles were not gone by 30 msw, even when the cortical blood flow had been completely obstructed (65).

If there were no other approach available it might nonetheless be reasonable to undertake deeper recompression in arterial gas embolism casualties who remain in cardiorespiratory arrest at 50 msw. However, there is a single factor which could explain the immediate deaths in the SETT series and which could be managed without resorting to extreme recompression. If the initial collapse of the patient is due to cardiac arrest, then vigorous and effective cardio-

pulmonary resuscitation would be required to prevent permanent anoxic or ischaemic damage to heart and brain. After recompression, intravascular bubbles could be cleared if cardiac output and perfusion pressure were sufficient. However, if the heart is in ventricular fibrillation, simply clearing the circulation of bubbles may not be enough to restore normal rhythm. Ventricular fibrillation is not likely to revert to normal rhythm without electrical countershock (28). Thus if fibrillation is the end result in some cases of arterial gas embolism, complete cardiopulmonary resuscitation facilities, including a defibrillator, will be required in addition to recompression to ensure a reasonable chance of successful treatment.

There is ample evidence in the literature to support the conclusion that ventricular fibrillation may be the factor which explains some treatment failures in arterial gas embolism, and that it can be caused either by embolisation of the coronary arteries or by an autonomic reflex originating in the embolised brain stem. (20,25).

CARDIAC ARRHYTHMIAS IN ARTERIAL GAS EMBOLISM

Direct evidence implicating coronary embolism in SETT deaths is lacking because of the ambiguity of bubbles in decompressed bodies. However, other case reports of gas embolism in humans can be found in which recompression was not undertaken. There is an extensive literature on the embolic complications of thoracic procedures such as empyema irrigation and induction of pneumothorax, mainly from the early part of this century. These phenomena are reviewed in depth by VanAllen et al (63) and Durant et al (16). These are interesting cases since they involve distribution of emboli via the pulmonary vein, as in SET casualties, but are not complicated by any hyperbaric exposure. Many of the fatal cases were shown at autopsy to have air in the coronary arteries, but from this alone, cause and effect cannot be deduced. Of greater interest are five cases described by Durant et al (16) in which

evidence of myocardial ischaemia is given. One death occurred suddenly but after chest pain had been reported. Coronary bubbles were found at post mortem. Two other patients died after some delay, and fresh myocardial infarcts were found despite patent coronary arteries. The bubbles had by that time been absorbed, but the ischaemic damage remained evident. Two survivors had experienced coma, but on regaining consciousness complained of chest pain. Electrocardiography demonstrated evolving ischaemic changes in both, including transient heart block in one. Other cases are described by VanAllen et al (63) and Chase (7). More recently, Thomas and Stephens (61) reported eight cases of gunshot and stab wounds of the chest in whom arterial gas was demonstrated at thoracotomy. Of the four of them who had coronary gas only one survived. Thus, evidence is available that coronary gas embolisation does occur and contributes to cardiac death. However, since these patients were not recompressed, one cannot say whether the process is reversible. Since ECG monitoring is now practicable in the SETT recompression chamber, it should be possible in the future not only to diagnose arrhythmias in the patients with persistent arrest, but also to detect unsuspected myocardial damage in those who recover with recompression.

Experimental studies in animals shed some light on the contribution of coronary embolism vs. central nervous system mechanisms. Some studies have been designed to simulate the pathophysiology of pulmonary barotrauma as it occurs in escape training and diving ascents. Others are more directed toward the previously described thoracic procedures, or, more recently, toward heart-lung machine accidents and other clinical problems.

Simulation of barotrauma has been effected by decompressing animals with their airways occluded (14,43,55), or by insufflation of air under pressure into their airways (3, 39,54). Both are better analogues for the diver or escape trainee who stops exhalation completely than one who has a smaller area of obstruction (40). The latter group may include half the casualties,

since that number are observed to exhale normally throughout the ascent.(17, 48). The degree of overexpansion of the lung required to cause embolism produces gross haemodynamic changes, including stasis or reversal of pulmonary arterial blood flow and incompetence of the pulmonic and tricuspid valves (39,55). Post mortem examination in these experiments usually shows, in addition to widespread arterial gas, gas in both sides of the heart and the great veins. Although death is rapid, the contribution of apnoea and brain damage cannot be separated from the direct coronary obstruction. Lenaghan et al (39) did see ventricular fibrillation with coronary air bubbles, but the arrhythmia followed a period of apnoea. Among this type of studies, only the experiments of Atkinson (3) used animals who were artifically ventilated, and his subjects survived extensive embolisation with no arrhythmia except a transient bradycardia. In these lung over-pressure experiments, then, coronary embolism is regularly seen, but cannot be identified unequivocally as the cause of death.

A more easily quantifiable technique for the simulation of embolism is the injection of air into the pulmonary vein or the left side of the heart. This type of study is generally done via thoracotomy, so direct visualisation of the coronary arteries is possible. Coronary embolisation is seen in almost all cases by this technique (16,22,33,47,63) and is concluded to be the cause of death, although widespread arterial emboli are seen elsewhere in the animal. Within 15 seconds of injection, coronary emboli are seen, the myocardium becomes pale, and arrhythmias are noted, including ST and T wave changes, Q waves and varying degrees of block (16,47,63). With sublethal doses, these changes reverse as the gas disappears. Lethal doses end in ventricular fibrillation or asystole after a period of profound dilatation. Injections into the left atrium (53) or left ventricle (24) produce similar results.

The distribution of gas following these injections is governed by the buoyancy of the emboli. If the animal is tilted head down, CNS signs are prevented,

but coronary embolism still occurs (33,47,63). A more direct means of eliminating CNS influences was attempted by VanAllen (63) and Rukstinat (53), who found that bubble traps inserted into the carotid arteries did not prevent the immediate cardiac effects. Death from coronary emboli also occurred when Rukstinat (53) ligated both carotid and vertebral arteries before injecting air in the atrium (a preparation which is viable in the dog for acute experiments). VanAllen et al (63) found that the head-up position prevented coronary embolism but still allowed cardiac arrest after a period of apnoea, which was attributed to CNS embolism. Moore and Braselton, however, found that a tilt of 30 degrees upward did not affect the proportion of coronary embolisation (47).

Thus it is clear that air passing through the left heart can cause immediate death due to myocardial ischaemia. The likelihood of coronary embolism is decreased in the head-up position in which submarine escape and diving ascents are made, but this cause of cardiac arrest in SET accidents must be considered a serious risk.

The indirect cardiac effects of brain embolism constitute another explanation for sudden death casualties. Evans and co-authors (20) have reviewed ways in which reflexes could initiate arrhythmias in such cases. Certainly, reflex cardiac arrhythmias have been demonstrated in response to experimental stimuli other than gas embolism. For example, Evans et al (19) have shown that head trauma in monkeys can cause A-V nodal rhythm and multifocal ventricular rhythms, and that these effects could be blocked by atropine. Manning and Cotten (44) described arrhythmias induced in cats by electrical stimulation of the diencephalon. These included ventricular tachycardia and could be prevented by blocking the vagi. Direct vagal stimulation, however, did not cause similar arrhythmias unless the stellate ganglion was stimulated at the same time. Groover and Stout (26), on the other hand, did succeed in causing ventricular fibrillation by vagal stimulation alone in baboons. In human patients, reflex

cardiac effects are thought to be a cause of mortality after intracranial hemorrhage and thrombosis (15,37,41,68). Experimental subarachnoid hemorrhage in dogs has been shown to cause ventricular tachycardia (18). In that study, the most severe arrhythmias occurred when both the sympathetic and vagal pathways were left intact. Conversely, blockade with both atropine and propranolol was required to abolish the arrhythmia. Mauck and Hockman (45) have reviewed the complex pathways by which these reflexes may come about. They report an experiment in which ventricular fibrillation was caused in dogs by brain stem stimulation and could be blocked by propranolol but not by section of the vagi.

Less is known about the role of CNS reflexes in sudden death from arterial gas embolism. Many investigators have reported cardiovascular changes in response to carotid injections of gas,(Fries et al (21), Geoghegan and Lam (22), Meldrum et al (46), deLavarde et al (13), de la Torre, Meredith and Netsky (11), Lyle and Fitzgerald (42), Waite et al (65), Pate and Birdsong (49), and Grulke (27)). In small doses, transient hypertension and bradycardia are seen, with minor disturbances of respiration. This may represent a Cushing reflex, since it is accompanied by an increase in CSF pressure (11,56). The fatal dose by this route is larger than that required in the pulmonary vein. Effective doses are directly compared by Kent and Blades (33), Geoghegan and Lam (22), Gomes et al (24), and by Rukstinat (53). Quantitative study of the effective carotid dosage is not enlightening, however, as the amount which actually enters the cerebral vessels is not controlled (11).

In an attempt to determine the role of brain stem embolism in possible reflex effects, the studies of Simms et al (56) and de la Torre, Mitchell and Netsky (12) are of interest. Simms et al injected directly into the vertebral artery in dogs, a sublethal dose which nonetheless produced arrhythmias such as bigeminy, and the ST-T wave changes of ischaemia. The group of de la Torre isolated the posterior circle of Willis with clips and found that carotid

embolism no longer produced cardiovascular changes, but vertebral injection did. Unfortunately, the dogs in the latter experiment were not artificially ventilated, so the apnoea occurring with vertebral embolisation is sufficient to explain the cardiac effects. Certainly, though, in SET casualties, artificial ventilation will prevent apnoea being the cause of death. Therefore the important information needed is whether brainstem embolism with ventilatory support can cause cardiac arrhythmias.

In the studies reviewed, where coronary embolism was prevented, few included ventilatory support. Gomes et al (24) caused death with carotid injections while the dog was ventilated, but the mode of death was not described. Babcock and Netsky (4) regularly observed arrhythmias after solid emboli, without respirator support, but when breathing was controlled the arrhythmias did not occur. In the study of Simms et al (56) the dose was deliberately sublethal, so a terminal arrhythmia was not seen. Whether a larger dose would have caused ventricular fibrillation or asystole remains an unanswered question. A preliminary report of experiments by Evans et al (20) appears to confirm that potentially lethal arrhythmias can occur in cats after carotid air injections even when ventilation is supported.

THERAPEUTIC IMPLICATIONS

The principal limitations upon therapy of SET casualties are inherent in the adverse environment of the recompression chamber. Most of these limitations have been overcome by experience and ingenuity. However, this report has shown why the provision of optimal cardiopulmonary resuscitation equipment and techniques is paramount in the effort to prevent future treatment failures in the category of immediate death. The main element missing from present equipment is a means to perform electrical countershock to terminate ventricular fibrillation. In order to provide this element safely, two daunting problems must be overcome. The first is that the elevated partial pressure of oxygen at

the treatment depth (1.2 bars at 50 msw on air) creates the hazard of a rapidly spreading fire if the defibrillator makes an electrical arc either within itself or against the patient. The second is that the patient will be wet from his ascent through the tank, and by contact, the attendant and the chamber will also be wet. Therefore the attendant would risk a potentially lethal electrical shock if the countershock current strayed from its intended path. These problems are so severe that existing techniques cannot be used in the chamber. But to apply countershock outside the chamber would be much less likely to help, and would in addition delay recompression. It is hoped that a purposeful research and development effort could produce defibrillating equipment which could be used with an acceptably low risk in the SETT recompression chamber.

In the event that the normal resuscitation efforts of closed-chest massage, artificial ventilation, defibrillation (when available), and correction of acidosis, fail to revert the arrhythmia to sinus rhythm, an additional specific recommendation can be made. From the evidence cited above, it is apparent that reflex-induced arrhythmia may be abolished by combined blockade with atropine and propranolol. This measure would be justified for a patient who continues in ventricular arrhythmia or heart block after the normal basic measures have been applied. Further research may provide a more refined pharmacologic approach to the reflex mechanism. It is certainly unwarranted at this time to suggest using autonomic blocking drugs to prevent the cardiac complications of brain stem embolism. Such a profound interference with the autonomic nervous system could very well make the trainee more susceptible to pulmonary barotrauma, by, for example, altering bronchiolar smooth muscle tone. That possible additional risk could clearly not be justified for the 57,000 trainees who did not have refractory cardiac arrest after SET ascents.

One further measure, while not specific for cardiac arrest, could be added to the treatment regimen. Increasing the partial pressure of oxygen during the

resuscitation would have three potentially salutary effects. First, the obvious further increase in alveolar oxygen would improve the oxygenation of arterial blood. Second, a high arterial oxygen tension has a powerful vasoconstricting effect on cerebral and other vascular beds. Since this effect is locally mediated, it does not vasoconstrict ischaemic tissue (5, 35, 58, 59, 60, 66). Therefore, a percentage of cardiac output could be diverted into the areas where flow is compromised. Finally, higher PO_2 means lower inert gas tension, and this could increase the gradient for elimination of the inert gas in the emboli.

The PO_2 could safely be increased during the resuscitation at 50 msw by breathing a suitable mixture through the breathing mask or ventilator already installed in the chamber. The duration of this added hyperoxia would need to be limited to prevent oxygen poisoning, but certainly two hours could be tolerated, especially if periodically interrupted (31). A standard Naval mixture consisting of 32.5% oxygen and 67.5% nitrogen is available and would increase the PO_2 to 1.95 bars. Helium-based mixtures should not be used for this purpose. There is evidence that helium could temporarily worsen the patient's condition by diffusing into the emboli and tissues more rapidly than the nitrogen already there could come out (10,36).

SUMMARY AND CONCLUSIONS

In 22½ years of Submarine Escape Training Tank operation at HMS DOLPHIN, 91 trainees have had incidents compatible with arterial gas embolism resulting from ascent through the tank. Recompression therapy was completely successful for 87 of these. Four fatalities were the only treatment failures. Two of the fatal cases showed initial relief but later deteriorated, eventually succumbing to the effects of cerebral oedema or possibly failure of microvascular reperfusion (the no-reflow phenomenon). Two of the patients, however, were apnoeic and pulseless at the outset, and showed no response to recompression. The mode of death and reasons for treatment failure in these two sudden deaths are the subjects of this report.

Electrocardiographic documentation is lacking in the two immediate fatalities. However, on the basis of indirect evidence, and both human cases and animal experiments reported in the literature, it is deduced that ventricular fibrillation was the terminal event. This cardiac catastrophe could be caused either by gas embolisation of the coronary arteries, or by autonomic reflex effects on the heart originating in the embolised brain stem. In either case, normal heart action would not probably be restored without electrical defibrillation, but this cannot be done safely at present in the SETT recompression chamber. Defibrillation would have a far greater chance of success when carried out at pressure than before recompression. It is concluded that the provision of safe electrical defibrillation and other optimal resuscitative equipment will increase the probability of salvaging future SET casualties from cardiac arrest.

Because of the possibility of reflex cardiac arrhythmias, refractory cases might benefit from autonomic blockade with parasympatholytic and β-sympatholytic drugs.

No compelling evidence has been found to suggest that increasing the therapeutic pressure above 6 bars could improve the outcome. However, the administration of a hyperoxic breathing mixture, such as 32.5% oxygen, 67.5% nitrogen, would improve oxygenation and might improve perfusion during the resuscitation.

RECOMMENDATIONS

I. Research and Development

A. The highest priority should be given to the development of a safe and effective method of electrical defibrillation compatible with the environment of a wet hyperbaric chamber at 6 bars pressure of air.

B. The electrocardiographic apparatus recently installed in the SETT recompression chamber should be used to obtain tracings on all casualties treated for coma and also those with chest pain. This should be done as soon as possible after onset, but not to interfere with primary therapy.

This study could provide important information as to the frequency of inapparent cardiac involvement and would also identify patients who deserve close monitoring for a time to ensure their recovery from transient myocardial ischaemia.

C. Experimental studies are in progress at the (US) Naval Medical Research Institute aimed at further clarification of the direct and reflex cardiac consequences of arterial embolism (20). These studies are included in the US-UK Memorandum of Understanding for a Co-operative Program on Diving Research and Development. No need is seen to duplicate these basic research efforts in the UK. The results should be monitored closely for any data, particularly regarding pharmacologic intervention, which would have a bearing on the management of SETT casualties.

II. Recommended Procedures for Management of the Pulseless SETT Casualty

A. Commence recompression to 50 m without delay.

B. Commence closed-chest cardiac massage and artificial ventilation as soon as possible.

C. Upon arrival of the MO, diagnose the cardiac rhythm by ECG.

D. Defibrillate if indicated.

E. Adminster 32.5% O_2/67.5% N_2 when possible during the resuscitation.

F. If cardiac arrest persists, administer appropriate intravenous fluids and drugs.

G. If ventricular arrhythmia persists despite repeated defibrillation, correction of acidosis, and other antiarrhythmic drugs, effect autonomic blockade with atropine and propranolol or the equivalent.

ACKNOWLEDGMENT

The author expresses his gratitude to Drs H V Hempleman, D H Elliott, and R R Pearson for encouragement and support; to Dr J M Hallenbeck for helpful suggestions; to the staff of SETT, HMS DOLPHIN for training data; to the library staff, Institute of Naval Medicine, for assistance with the references; and to Mrs Mary Hathaway for assistance with the manuscript.

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APPENDIX

CASE SUMMARIES

Case 58

This 19 year old trainee stopped exhaling temporarily about half way through his 9-metre buoyant ascent. Upon surfacing he exhaled loudly and immediately lost consciousness. He was pulled from the water and recompressed immediately to 50 msw equivalent pressure. At pressure, the chamber attendant began expired air ventilation with good effect as judged by the patient's chest movement. The medical officer reached the patient approximately 5 minutes after the incident began, and found him pulseless and apnoeic, but not cyanotic. Auscultation revealed good air movement but no heart sounds. Closed-chest cardiac massage was then begun and the chamber was further compressed to 70 msw, its maximum working pressure. An intracardiac injection of 1 ml of 0.1% epinephrine was given; no other drugs are noted on the record. After 30 minutes of resuscitation at this depth, the patient was pronounced dead.

Post mortem examination was performed approximately 4 hours later. Notable findings included subcutaneous emphysema of the neck; gas bubbles in the great vessels of the neck, the internal carotid arteries, the middle cerebral arteries, and the coronary arteries; a small amount of fluid and air in the pericardium; needle marks on the left ventricular wall; bilateral pneumothorax; and petechial hemorrhages on the pleural surfaces of both lungs, as well as a few larger subpleural hemorrhages measuring up to 2 x 5 cm. Bubbles were not seen in the surface vessels of the brain. The brain was congested but otherwise macroscopically normal.

Case 123

This 20 year old trainee made an apparently normal hooded ascent from 30 metres, then moved to the ladder and lost consciousness. He was pulled out and recompressed immediately to 50 msw, accompanied by the medical officer and another attendant. The patient was apnoeic, pulseless, and initially opisthotonic. Closed chest cardiac massage and expired air ventilation were begun, then interrupted as the patient took four or five breaths, and then resumed as the patient became apnoeic again.

At 16 minutes after the incident began, an intravenous infusion of 4.2% sodium bicarbonate was begun and 1 ml of 0.01% epinephrine was given by intracardiac injection. The epinephrine was repeated five minutes later along with 10 ml of calcium gluconate. There having been no response to these efforts, the patient was pronounced dead 26 minutes after the incident began.

Post mortem examination was performed three days later. Notable findings included gas bubbles in the cerebral veins and carotid arteries; flattening of the cerebral convolutions and coning of the base; numerous sub-pleural blebs up to 1 cm in diameter; oedema and congestion of the lungs; and small bubbles of gas in the mediastinum without pneumothorax. No abnormality of the heart was mentioned.

W O R K S H O P

on

ARTERIAL AIR EMBOLISM

AND

ACUTE STROKE

held on

Friday, 13 May, 1977
Toronto, Canada
(preceding the UMS Annual Scientific Meeting)

John M. Hallenbeck
Leon J. Greenbaum, Jr.
Chairmen and Editors

This workshop was supported by the National Institute of Neurological Diseases and Stroke and by the Office of Naval Research.

The publication of the workshop report was supported by the National Library of Medicine, National Institutes of Health, Public Health Service, Department of Health, Education and Welfare.

IMPAIRED MICROVASCULAR PERFUSION AND SECONDARY DETERIORATION IN DYSBARIC CEREBRAL AIR EMBOLISM

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There is a strange and catastrophic phenomenon that has been observed repeatedly in cases of dysbaric cerebral air embolism occurring during submarine escape training. Characteristically, a trainee breaks surface after a training tower run and shortly thereafter loses consciousness. After one to several minutes, he is rapidly recompressed to a simulated depth of 165 ft with air as the breathing medium. The trainee will generally regain consciousness within 10 minutes of reaching a simulated depth of 165 ft. He becomes alert with a clear sensorium and no evidence of neurologic dysfunction to clinical examination by a medical officer. However, 20 minutes to 2 hours after this initial recovery, a secondary deterioration of clinical status sets in. If the victim had originally presented with a focal deficit, the same deficit may reappear. If loss of consciousness had been the initial event, headache, confusion, blindness, and seizures form a common constellation of symptoms and signs during the recurrence.

It is a testable possibility that secondary deterioration in these cases results from a progressive impairment of microvascular perfusion that evolves after brain blood flow has been initially restored by recompression. However, should this hypothesis prove correct, the development of impaired microvascular reperfusion after only one to several minutes of multifocal ischemia will require additional explanation since central nervous system ischemia of such brief duration induced by other means has not generally been accompanied by impaired reflow (7,13). Of particular relevance to ischemia caused by air embolism, however, is the fact that studies in several laboratories suggest that intravascular gas may directly produce endothelial damage that is not mediated through hypoxia or ischemia (12,18).

Naval Medical Research and Development Command, Research Task No. M0099.PN001.1158. The opinions and assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large. The experiments conducted herein were conducted according to the principles set forth in the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Resources, National Research Council, DHEW, Pub. No. (NIH) 74-23.

Progressive deterioration of local blood flow has been noted in experimental models of spinal cord trauma (5,6,17) and foci of ischemic neuronal damage have been seen in histopathologic analyses of head injury cases (8). Impairment of microvascular reperfusion has been observed in experimental models of reversible central nervous system ischemia (1,3). Considered together, these observations suggest a general concept of flow disruption in regions of acute tissue damage. Studies in which intravascular blood appeared to adversely influence post-ischemic reperfusion (11,14) introduce the possibility that blood has a positive role in this local flow disruption. It is conceivable that blood contains a factor or factors capable of interacting in zones of acute tissue damage to progressively impair nutrient flow (9). In order to investigate this possibility, we have employed the cerebrospinal fluid (CSF) compression ischemia model with the CSF pressure set at mean arterial pressure during the ischemic interval (10). This pressure relationship permits blood to enter the central nervous system vessels as arterial pressure rises briefly above CSF pressure during systole. Since the duration of systole is much less than the mean transit time of the cerebral circulation (15), the blood in central nervous system vessels recedes as arterial pressure falls below CSF pressure during diastole. The overall effect is a cyclic influx and efflux of blood into and out of vessels to the neuraxis coincident with fluctuations of systemic arterial pressure but with no net flow. Autoradiographic blood flow studies performed with the CSF pressure equal to mean arterial pressure have demonstrated that central nervous system circulation is arrested under these conditions (Figure 1).

Detailed discussion of the experimental model has been presented elsewhere (9,10). In brief, dogs were anesthetized with sodium pentobarbital 25 to 30 mg/kg, intubated and ventilated by a respirator. End-tidal P_{CO2} and core temperature were continuously monitored and blood gases were periodically measured. The femoral vessels were catheterized bilaterally and both aortic pressure and right ventricular pressure were monitored during the course of the experiments. The animals were anticoagulated with heparin 300 units/kg i.v. A needle was percutaneously placed in the cisternal space and connected to a line containing Elliott's solution B, a mock cerebrospinal fluid which was warmed to 38° C before infusion. Ischemia was induced by raising the bottle containing Elliott's solution B until hydrostatic pressure in the CSF line equaled mean systemic arterial pressure. In several groups of animals, three glass-wool filters in succession were inserted into an arterio-venous shunt from femoral artery to femoral vein and the animal's blood was filtered for one hour prior to induction of ischemia. The purpose of this operation was to permit those elements of blood which react with a foreign surface to interact with the glass. The glass-wool filters were made by dividing the filter-housing of a Fenwall blood recipient set, removing the dacron mesh and inserting into each housing half loosely packed, washed, pyrex glass-wool. The two halves were then rejoined with a collar made of Tygon® tubing.

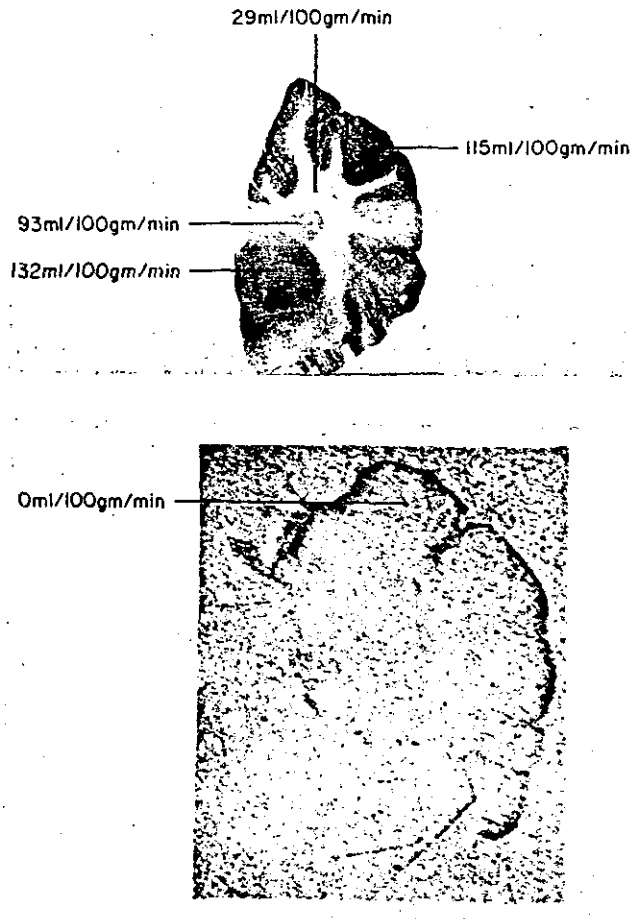

Figure 1. The upper autoradiogram shows uniformly excellent perfusion in a section of brain. This section is from an animal exposed to glass-wool filtration, followed by 35 minutes of CSF-compression ischemia and 30 minutes of general neuraxis reflow. The lower autoradiogram is from an animal in which the ^{14}C-antipyrine autoradiographic blood flow study was performed during CSF-compression ischemia with CSF pressure equal to mean arterial pressure. Brain circulation has been arrested.

There are essentially 4 stages in the experimental design. Following preparation of the animal, a stage of either observation or glass-wool filtration is carried out for one hour. The next stage involves CSF compression ischemia and lasts 35 minutes. The third stage involved lowering the CSF pressure to 10 mmHg (136 cmH_2O), controlling systolic blood pressure between 110 and 120 mmHg and allowing 30 minutes of recirculation to the neuraxis. The final stage is a one minute ^{14}C-antipyrine autoradiographic blood flow assay (19).

The initial series compared the effects of this protocol on a group of 5 heparinized dogs vis-a-vis a group of 5 heparinized dogs whose blood had in addition been filtered through glass-wool for one hour prior to central nervous system ischemia. Table 1 shows the average blood flows in various neuroanatomic areas and heart in the 2 groups. The higher flows in brain structures of the filtered group are obvious and the differences are generally significant at the 0.05 level by 2 tail Student t-test. Animals given heparin alone had focal areas of very low flow which are felt to correspond to zones of impaired microvascular reperfusion noted in other models (1,3). In contrast, filtered animals had uniformly excellent reflow without focal zones of impaired reperfusion (Figure 2). These studies indicate that modification of an animal's blood by exposure to glass-wool prior to causing central nervous system ischemia greatly enhances post-ischemic brain reflow.

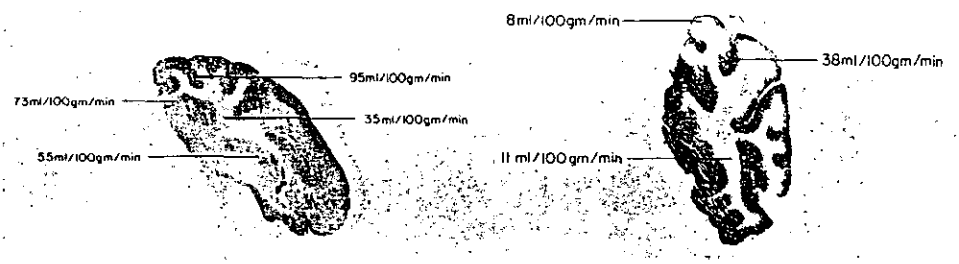

Figure 2. Two autoradiograms of posterior cerebral hemispheres. The autoradiogram on the left is from an animal that received glass-wool filtration and shows uniform reperfusion. The autoradiogram on the right is from an animal given heparin without glass-wool filtration and shows low post-ischemic flows with focal zones of impaired reperfusion.

Table 1

LOCAL BLOOD FLOWS IN VARIOUS NEUROANATOMIC AREAS AND HEART IN ML PER 100 GM PER MINUTE

(MEAN ± SEM)

	Group 1 (non-filtered)	Group 2 (filtered)	Significance of difference*
Anterior Centrum Ovale	13 ± 4	28 ± 1	$p < 0.01$
Auditory Cortex	46 ± 11	108 ± 14	$p < 0.005$
Caudate Nucleus	51 ± 16	101 ± 10	$p < 0.05$
Corpus Callosum	16 ± 6	31 ± 2	$p > 0.05$
Hippocampus	30 ± 9	81 ± 17	$p < 0.02$
Internal Capsule	19 ± 6	35 ± 2	$p < 0.05$
Middle Centrum Ovale	12 ± 4	31 ± 1	$p < 0.005$
Optic Radiations	13 ± 4	32 ± 2	$p < 0.005$
Sensorimotor Cortex	39 ± 6	123 ± 17	$p < 0.001$
Thalamus	44 ± 12	106 ± 11	$p < 0.005$
Visual Cortex	40 ± 10	101 ± 14	$p < 0.02$
Posterior-middle Cerebral Watershed Cortex	16 ± 7	119 ± 20	$p < 0.001$
Anterior-middle Cerebral Watershed Cortex	31 ± 6	93 ± 11	$p < 0.005$
Anterior Association Cortex	38 ± 7	103 ± 24	$p < 0.02$
Spinal Cord Gray	48 ± 17	26 ± 4	$p > 0.05$
Spinal Cord White	18 ± 2	15 ± 4	$p > 0.05$
Heart-Left Ventricle	281 ± 88	231 ± 30	$p > 0.05$

*By 2-tail Student t-test.

In order to investigate further the possibility that the glass-wool removes or inactivates a normal constituent of blood, we infused plasma fractions after glass-wool filtration but before rendering the neuraxis ischemic. It was assumed that if a plasma fraction contained a constituent deleterious to reflow, adding that fraction after glass-wool filtration would nullify the beneficial effect of filtration and restore the defect in reperfusion. The results of adding 1) cryoprecipitate, 2) a plasma concentrate containing molecules in excess of 10,000 molecular weight (MW), and 3) a plasma ultra-filtrate containing molecules of less than 10,000 MW will be described.

Cryoprecipitate was the first fraction added. It was chosen because of its detrimental effect on ex-vivo kidney perfusion (2). One-thousand milliliters of pooled dog blood was spun at 4,000 x G for 15 minutes at 25° C. The supernatant was recovered, then spun at 18,000 x G for 60 minutes at 25° C. The cell-free supernatant plasma was recovered and frozen in a slurry of methanol and dry-ice. One day prior to the experiment, the plasma was placed in a refrigerator at 4° C and on the morning of the experiment the thawing plasma was spun as a slushy liquid at 18,000 x G for 60 minutes at 4° C. The supernatant was decanted and discarded. The cryoprecipitate was redissolved in 45 to 60 cc of saline at 38° C and infused into each of 5 animals after glass-wool filtration. Table 2 compares the average blood flows in various neuroanatomic structures after 35 minutes of CSF compression ischemia followed by 30 minutes of general neuraxis recirculation in 2 groups of 5 dogs each. Addition of the plasma constituents contained in the cryoprecipitate fraction nullified the beneficial effects of glass-wool filtration.

In a second series of experiments, cell-free plasma was obtained from 1000 ml of pooled dog blood. The plasma was then concentrated from an initial volume of about 550 ml to about 200 ml by filtering out water and molecules of less than 10,000 MW in an Amicon® ultrafiltration system. An average of 200 ml of concentrated plasma was infused intravenously into each of 3 dogs after glass-wool filtration. In Table 3 the group of 3 animals in which the greater than 10,000 MW plasma concentrate was added after glass-wool filtration is compared with the group of 5 animals subjected to glass-wool filtration alone. The average flows in the plasma concentrate group are generally lower and in a number of cortical areas, the differences are significant despite the small sample size. Animals in which cryoprecipitate was added as well as those in which the greater than 10,000 MW plasma concentrate was added demonstrated focal areas of extremely low flow characteristic of impaired microvascular reperfusion.

In a final experiment, 200 ml of plasma ultra-filtrate containing molecules of less than 10,000 MW obtained by means of the Amicon® ultrafiltration system were infused into a dog after glass-wool filtration. Reflow was uniformly excellent and directly comparable with animals whose blood has been exposed to glass-wool filtration without subsequent infusion of a plasma fraction.

In summary, modification of an animal's blood by exposure to glass-wool prior to causing central nervous system ischemia greatly

Table 2

LOCAL BLOOD FLOWS IN VARIOUS NEUROANATOMIC AREAS AND HEART IN ML PER 100 GM PER MINUTE (MEAN ± SEM)

	FILTERED	CRYOPRECIPITATE ADDED	SIGNIFICANCE OF DIFFERENCE*
Anterior Centrum Ovale	28 ± 1	13 ± 5	$0.05 < p < 0.10$
Auditory Cortex	108 ± 14	33 ± 7	$p < 0.02$
Caudate Nucleus	101 ± 10	48 ± 17	$p < 0.05$
Corpus Callosum	31 ± 2	15 ± 5	$p < 0.02$
Hippocampus	81 ± 17	32 ± 8	$p < 0.02$
Internal Capsule	35 ± 2	28 ± 7	$p > 0.10$
Middle Centrum Ovale	31 ± 1	16 ± 6	$0.05 < p < 0.10$
Optic Radiations	32 ± 2	16 ± 6	$p < 0.05$
Sensorimotor Cortex	123 ± 17	31 ± 2	$p < 0.01$
Thalamus	106 ± 11	65 ± 21	$0.05 < p < 0.10$
Visual Cortex	101 ± 14	34 ± 15	$p < 0.05$
Posterior-Middle Cerebral Watershed Cortex	119 ± 20	30 ± 14	$p < 0.01$
Anterior-Middle Cerebral Watershed Cortex	93 ± 11	24 ± 12	$p < 0.02$
Anterior Association Cortex	103 ± 24	36 ± 15	$p < 0.05$
Spinal Cord Gray	26 ± 4	54 ± 11	$0.05 < p < 0.10$
Spinal Cord White	15 ± 4	22 ± 6	$p > 0.10$
Heart-Left Ventricle	231 ± 30	175 ± 17	$p > 0.10$

*BY WILCOXON RANK SUM TEST

Table 3

COMPARISON OF > 10,000 MW PLASMA CONCENTRATE ADDITION (N=3) AND GLASS WOOL FILTRATION (N=5) *LOCAL BLOOD FLOWS IN VARIOUS NEUROANATOMIC* AREAS AND HEART IN ML PER 100 GM PER MINUTE (MEAN ± SEM)

	Filtered	Plasma Concentrate	Significance of Difference*
Anterior Centrum Ovale	28 ± 1	19 ± 9	$p > 0.05$
Auditory Cortex	108 ± 14	42 ± 11	$p < 0.05$
Caudate Nucleus	101 ± 10	63 ± 19	$p > 0.05$
Corpus Callosum	31 ± 2	25 ± 12	$p > 0.05$
Hippcampus	81 ± 17	46 ± 18	$p > 0.05$
Internal Capsule	35 ± 2	29 ± 9	$p > 0.05$
Middle Centrum Ovale	31 ± 1	19 ± 6	$p > 0.05$
Optic Radiations	32 ± 2	19 ± 2	$p < 0.01$
Sensorimotor Cortex	123 ± 17	34 ± 8	$p < 0.02$
Thalamus	106 ± 11	68 ± 17	$p > 0.05$
Visual Cortex	101 ± 14	38 ± 8	$p < 0.05$
Posterior-Middle Cerebral Watershed Cortex	119 ± 20	30 ± 13	$p < 0.05$
Anterior-Middle Cerebral Watershed Cortex	93 ± 11	25 ± 7	$p < 0.02$
Anterior Association Cortex	103 ± 24	46 ± 11	$p > 0.05$
Spinal Cord Gray	26 ± 4	46 ± 3	$p < 0.05$
Spinal Cord White	15 ± 4	22 ± 6	$p > 0.05$
Heart-Left Ventricle	231 ± 30	121 ± 21	$p < 0.05$

*By 2-tail Student t-test.

enhances post-ischemic brain reflow. Further, pooled homologous dog plasma contains activity deleterious to post-ischemic reflow. This activity is found in cryoprecipitate as well as in the fraction containing molecules in excess of 10,000 MW. An ultra-filtrate of pooled plasma containing molecular species of less than 10,000 MW did not interfere with post-ischemic reperfusion.

To draw the foregoing discussion together into a speculative conclusion, we would like to suggest the possibility that pathologic events in dysbaric air embolism could converge to produce impairment of microvascular perfusion in brain and consequent secondary deterioration of clinical status. Several derangements could lead to a decrease in cardiac output. Expansion of mediastinal gas during decompression from 165 ft could lead to interference with either venous return or flow through the lungs. Another possible derangement lowering cardiac output would be increased pulmonary vascular resistance arising from injury incurred during the initial pulmonary barotrauma. Other pathologic events might include the development of brain edema, release of vaso-active substances from damaged lungs and further gas embolization. Any of these pathologic events could contribute to a slowing of cerebral circulation and work by Denny-Brown and Meyer (4) and by Osborne and Halsey (16) suggests that in areas of acute ischemic brain damage slow flows can progressively shut down. Our work indicates this process of progressive shutdown of nutrient flow could involve an interaction between some plasma factor or factors and acutely damaged neural tissue. Identification of such putative plasma factors and their therapeutic inactivation might therefore benefit cases of dysbaric cerebral air embolism complicated by secondary deterioration.

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DISCUSSION

Dr. Bourke: I would like to ask you a question with regard to this specific research. As I recall, there is a factor in blood called Hageman factor or glass factor, that is, it is activated when it contacts glass. Is that the factor specifically that you are pulling out or not? Does the blood clot after it has passed through glass-wool?

Dr. Hallenbeck: That's a very important question. When we began filtering the blood, the concept was that we would adsorb proteins or some other molecule onto the glass and strip them out of the blood. However, that is not the only possibility. Hageman factor is certainly getting activated and the animals are heparinized so that this activation does not proceed to clotting. Activation of Hageman factor ramifies and leads to activation of other systems such as the fibrinolytic system, the complement system and the kinin system, for example. These systems exist in a dynamic equilibrium with enzymes that make active substances from precursors and enzymes that degrade the active molecules. Quite possibly we are causing a consumptive depletion of some system instead of stripping some active molecule out of the blood. We have not clarified that yet. We could also be activating or introducing an inhibitor.

Unidentified: What were your platelet counts before and after the blood passed through the glass-wool filters?

Dr. Hallenbeck: The platelet counts characteristically fall to within 1/2 to 2/3 of the original level. The counts do not fall into the range where one would attribute the results to thrombocytopenia.

Dr. Halsey: John, do you have any information about the recovery of the EEG or evoked potentials in these animals?

Dr. Hallenbeck: No, we don't. Our only index has been blood flow.

Dr. Halsey: As I understand these problems, it would be critical to know whether or not the microcirculatory occlusion occurs only after the brain cells have died.

Dr. Hallenbeck: I am not sure that ours is the best approach, but we have been considering this model as an assay system and have not made an attempt to model something that occurs clinically in humans. The ultimate goal is to identify some molecule (or molecules) in plasma which is involved in the interaction that leads to impaired microvascular perfusion and later, to eliminate or inactivate this molecule in a model of focal ischemia such as internal carotid air embolism or clipping of the middle cerebral artery. We would then evaluate the effect of inactivating this molecule on graded ischemic

insults in focal ischemia. At this stage we would use such neurophysiologic indices of neuronal function as the EEG and evoked responses.

Dr. Ah See: John, why don't you postulate a viscosity effect?

Dr. Hallenbeck: We have a Wells-Brookfield microviscometer and we have measured whole blood viscosity and it does not change.

Dr. Greene: There is a recent paper from another field investigating problems that occur in pulmonary blood flow during hemodialysis in which interaction of the blood with a cellophane membrane activates complement and leads to pulmonary hypertension. Inactivation of the complement prevented the pulmonary hypertension.

Dr. Hallenbeck: Yes, that is a good point. He is mentioning that in hemodialysis the cellophane membrane activates the C5A component of the complement system and causes leukostasis in the lungs and a consequent increase in pulmonary artery pressure. So we recently checked complement levels in our model using a sheep red cell hemolysis assay and this rather gross assay indicated that we were not decomplementing the animals by filtering their blood through glasswool.

Dr. Greene: Could I just make one other comment relative to recompression? We have been talking about the possibility that the timing of recompression might have an adverse effect. That is certainly speculative and clearly recompression is the only treatment guaranteed effective in air embolism. Interestingly, in one study I reviewed, in which air embolism was modeled in the dog, air was observed in the pial vessels 48 hours after the embolism. It therefore seems possible that recompression could still remove bubbles even in a case that arrived after some delay at a recompression chamber. The option of not recompressing to avoid these other complications really should not be considered until a lot more is known about the basic mechanisms.

ABSTRACT

Macklin, Madge Thurlow and Charles C. Macklin

Malignant interstitial emphysema of the lungs and mediastinum as an important occult complication in many respiratory diseases and other conditions. An interpretation of the clinical literature in the light of laboratory experiment. Medicine 23:281-358. 1944.

This is an extensive and comprehensive article which covers both experimental and clinical aspects of pneumomediastinum with 337 literature citations. The authors differentiate between the benign and malignant forms of the condition on the basis of degree of severity of the condition. They conclude that there are many clinical cases in which the presence of air in the tissues of the lung is not suspected, and in which its effects have been regarded as being produced by the primary disease itself, rather than by the interstitial air. In other cases air is recognized as being present in the pleural cavities, in the subcutaneous tissues of the neck, trunk, etc., in the retroperitoneal spaces or in the peritoneal cavity. The method and route of escape of air is misunderstood in such cases, but may cause death through airblock, if it is not removed. Atelectasis of some part of the lung, followed by hyperinflation in adjoining regions of the same lung or in the opposite lung, general overinflation with or without increased intra-alveolar pressure, and decreased blood supply to the pulmonary vessels either with increased intra-alveolar pressure, or with hyperinflation are conditions which lead to entrapment of air in lung tissue. In these three classes, air escapes through ruptured alveolar bases into the sheaths of the pulmonary vessels, producing one or more of the following: air in the mediastinum; in the thoracic cavity; in the subcutaneous tissues of the face, neck, chest, axillae and body; in the retroperitoneal spaces from whence it may rupture into the peritoneal cavity; around the pericardium, in which event a pericardial knock is heard. Clinically, dyspnoea and cyanosis occur owing to a rise in mediastinal pressure and fixation of the chest in maximal or submaximal inspiration position. The air then distends the mediastinum, or invades the connective tissue septa of the lung. The air may gradually be resorbed, and the patient recover, or it may increase in severity and the patient may die. The precipitating cause of this train of events may occur in a wide variety of conditions, but is always a pressure gradient from air in the alveoli to perivascular sheath or underlying septa, leading to alveolar rupture and formation of pulmonary interstitial emphysema. Air leaks cause bubbles which press upon the small pulmonary vessels occluding their lumina and producing airblock; may leak into the interlobular connective tissue, causing airlock, or may follow along vessel sheaths ending up in areas around heart, neck, face, axillae, abdomen, etc. If it ruptures the mediastinal wall, pneumothorax results. Pain, respiratory function, circulation and cardiac function are seriously affected.

Factors predisposing to leakage are apparently toxins of certain infectious diseases, particularly influenza; and perhaps an inherited constitutional weakness of the alveolar walls.

When air escapes from the mediastinum into the subcutaneous tissues, or into the retroperitoneum or even into the pleural cavities, provided that it does not produce a bilateral pneumothorax, or a tension pneumothorax, the condition is likely to be benign, since the pressure in the mediastinum is relieved. If the leak continues, and builds up higher pressures in the mediastinum than can be relieved by the avenues of escape, the condition, originally benign, may become malignant. Air in the mediastinum and interstitial tissues of the lung may be occult, unrecognized by means of visible manifestations and hence potentially fatal. It accompanies a wide variety of clinical conditions and respiratory diseases.

J. Path. Bact. 82:198-202. 1961.

THE EFFECTS OF A RAISED INTRAPULMONARY PRESSURE ON THE LUNGS OF FRESH UNCHILLED CADAVERS

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Royal Naval Physiological Laboratory, Alverstoke, Hants

(PLATES LXIV AND LXV)

Wright (1950) reported cases of burst lung in members of the crew of a submarine sunk in 40 ft of water; unfortunately there was some delay in recovering the victims, and it was consequently difficult to establish the extent of the lung damage. There was, however, sufficient evidence to suggest that rupture of the visceral pleura had occurred in most of the victims, whether or not they had used Davis Submarine Escape Apparatus for their ascent to the surface.

There is no information on the pressures at which human lungs rupture during life; it was, therefore, planned to determine this in fresh unchilled cadavers, although it was appreciated that the behaviour of corpse lungs and their associated tissues in response to stress might be different from that of living lungs.

Polak and Adams (1932) had shown that high intratracheal pressures could be tolerated in dogs if the chest and abdomen were both bound. It was, therefore, considered worthwhile to repeat these observations on cadavers.

METHOD

It had been proposed to use fresh, preferably young, bodies, in which there was no suspicion of pulmonary abnormality. During the period in which arrangements had been made to carry out these experiments comparatively few young bodies became available and several of these could not be used, since they were either known to have pathological changes in the lungs, or were involved in some medico-legal case. Only 5 bodies could be used for these studies; they were those of persons aged between 27 and 64 years.

The experimental arrangement is shown diagrammatically in fig. 1.

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The whole assembly was mounted on a mobile trolley for use in the post-mortem room. The head of the subject was supported on the post-mortem table with the neck extended as much as possible. A midline incision approximately 3 in. (7·5 mm.) in length was made in the neck to expose the trachea, which was then freed by careful blunt dissection; any small vessels damaged

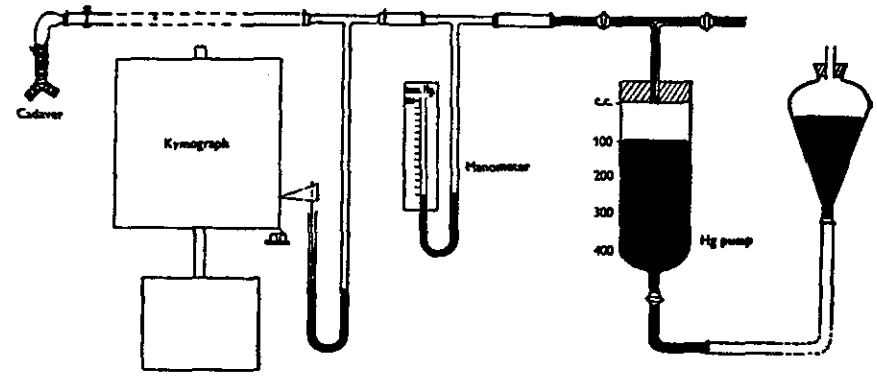

FIG. 1.—Schematic drawing of the apparatus used for raising the intrapulmonary pressure in cadavers.

were ligated. A cannula of suitable size was inserted into the trachea and then a few inches of $\frac{3}{4}$ in. wide tape wound over the trachea to prevent cutting by the ligatures subsequently applied; the cannula was connected to the recording apparatus by rubber pressure-tubing. Known volumes of air, measured at atmospheric pressure and at *c.* 18°C., were injected into the trachea by means of a mercury pump; the intratracheal pressure was continuously recorded on a kymograph. 200 ml. of air were injected at a time into the trachea at the rate of 20 ml. per sec. After each injection, a careful watch was kept on the

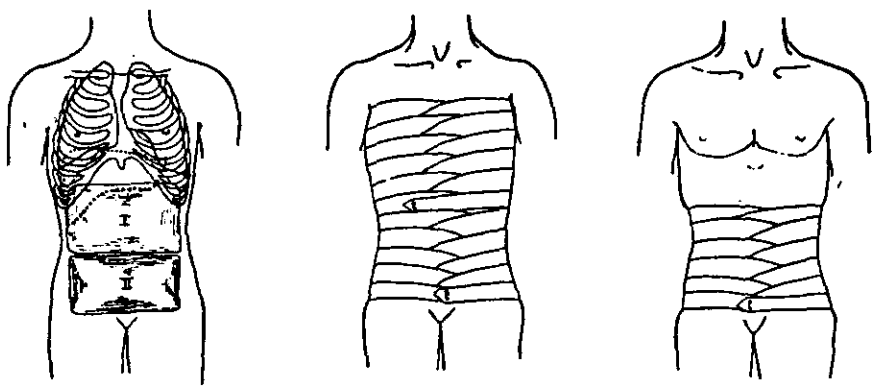

FIG. 2.—Schematic drawing of chest and abdomen bound with many-tailed bandages. Position of sandbags is also shown.

kymograph tracing for any sudden or gradual drop in pressure which would indicate a breakdown in the pulmonary tissue; the intratracheal pressure was then reduced to atmospheric.

In three cadavers, the chest and abdomen were bound with many-tail bandages before the experiment, in one the abdomen only was bound, and in the remaining one no binding was used. In order to minimise downward movement of the liver and spleen two sandbags were placed over the abdominal wall (fig. 2) and many-tailed bandages were then tightly applied over them. The

presence of air in the pleural cavities was detected by making a small water-trap in the lateral chest wall on each side, resecting a small piece of rib subperiosteally, and carefully nicking the exposed parietal pleura below the fluid level.

The chest was then opened by dividing the costal cartilages with guillotine-type shears (Goertz-Stille). After the large blood vessels had been clamped, heart, mediastinum and lungs were removed and transferred to a water-bath. A small quantity of air was injected into the trachea in order to distend the lungs slightly; these were then gently manœuvred under the fluid in order to detect any sites of leakage.

Results

The types of pressure tracings obtained during inflation of the lungs are shown in fig. 3. None of these showed any dramatic drop in pressure. A common characteristic in all these tracings was that, after each volume of air had been injected, there was a slow fall in pressure for a few seconds before it settled down to a constant level. As the intratracheal pressure was raised, it took longer to settle down. If the drop in intratracheal pressure continued, it was assumed that some type of injury had occurred in the lungs, and no more air was injected. Necropsy findings showed evidence of pulmonary barotrauma in all such cases.

Owing to the wide range of pathological changes among the limited number of subjects used for this study, the necropsy findings relating to the chest are given for each cadaver separately.

Case 1, *female, age* 47 (*unbound*). The intrapulmonary pressure reached a maximum of 93 mm. Hg after 6·3 litres of air had been injected. Before this pressure was reached, a considerable amount of fæces and urine had been forced from the body by the deflection of the diaphragm. At necropsy a fair quantity of air bubbled through the trap on the right side, but none escaped from the left pleural cavity. The subcutaneous tissues in the neck contained a small quantity of air, but it was not widespread.

When the chest was opened, the lungs were found to be voluminous and did not collapse when the trachea was opened. The connective tissues of the anterior mediastinum showed the presence of trapped air. Both lungs showed several diaphragmatic adhesions. Examination under water showed several pin-hole leaks near the basal adhesions on the right side. No leakage of air occurred from the left lung. This was a case of pneumothorax with rupture of the right lung.

Case 2, *male, age* 64 (*abdomen bound*). The intratracheal pressure rose to a maximum of 80 mm. Hg after 5·8 litres of air had been injected. At necropsy no air leaked through the traps from either pleural cavity. The anterior mediastinum and associated structures contained large pockets of air and the lungs filled the thoracic cage. No blood or excess fluid was found in the pleural cavities. Several large emphysematous bullæ were found over the anterior surface of the right lung (fig. 4) and along the anterior medial border of the left basal lobe. During the removal of heart and lungs, several small adhesions had to be divided along the dorsal border of the left lung. No rupture of visceral pleura was detected when the lungs were examined under water, but a considerable amount of air escaped from the loose connective tissues between the parietal layers of pleura and pericardium. Diagnosis: pulmonary interstitial emphysema.

Case 3, *female, age* 27 (*abdomen and chest bound*). In this case the maximum intrapulmonary pressure was 190 mm. Hg (fig. 3), and the total volume of air injected was 6·2 litres. Considerable congestion of the face and neck developed and marked interstitial emphysema was seen over the upper part of the thorax and arms by the time the last injection was given. Tapping the pleural cavities revealed no leakage of air from either side. The lungs were very voluminous. No blood or excess fluid was found in the pleural cavities and no adhesions were present. The exposed surface of the lungs showed scattered areas of petechial

PULMONARY BAROTRAUMA IN CORPSES

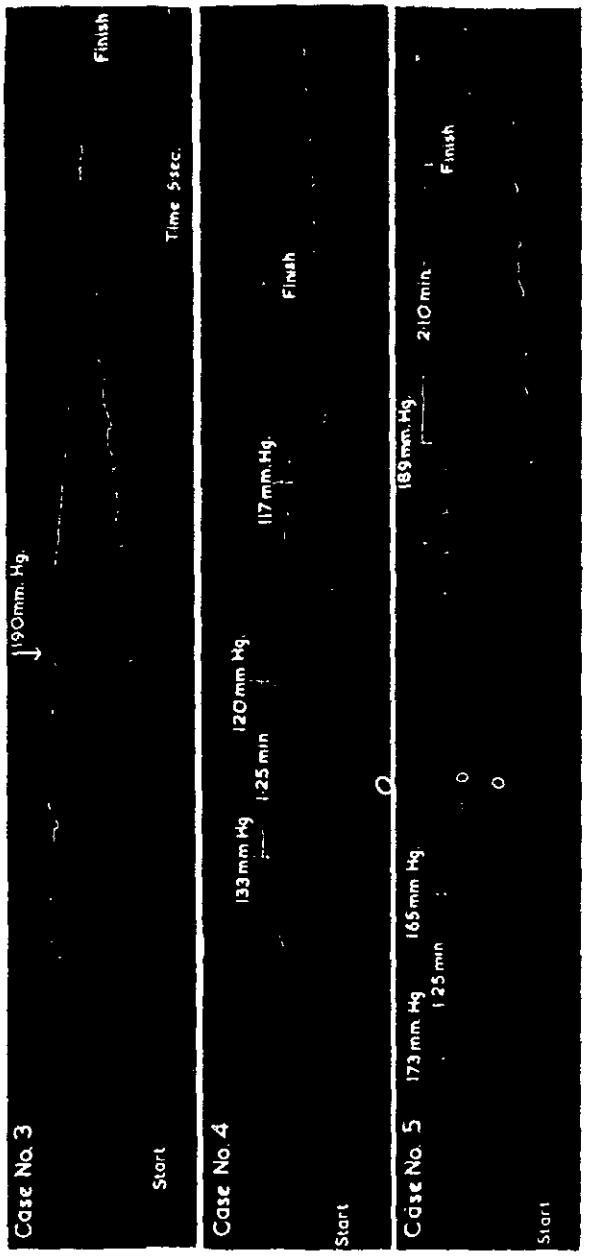

FIG. 3.—Intratracheal pressure tracings in cadavers with chest and abdomen bound.

PULMONARY BAROTRAUMA IN CORPSES

FIG. 4.—Lung of a cadaver, where intratracheal pressure was raised after the abdomen had been bound, showing emphysematous bullæ.

FIG. 5.—Lung of a cadaver, where intratracheal pressure was raised after both the chest and abdomen had been bound, showing emphysematous bullæ.

hæmorrhage. When the lungs were examined under water several large bubbles of air escaped from the loose connective tissue near the parietal pleura and pericardium. This also was a case of interstitial emphysema.

Case 4, *male, age* 61 (*abdomen and chest bound*). The intrapulmonary pressure was raised in steps to a maximum of 133 mm. Hg after 7·6 litres of air had been injected (fig. 3). A considerable amount of interstitial emphysema was present in the neck, upper thorax and arms. When the cervical incision was extended downwards over the chest to the xiphisternum, air was heard leaking from the cut surfaces. Minute bubbles of air escaped freely through a small quantity of water placed in the incision. In this case, air under pressure in the anterior mediastinum had passed to the ventral surface of the sternum intercostally. When the sternum was deflected, large tracts of air were seen along the mediastinal cleft and extending over the pericardium. No air leaked from the pericardial sac when it was opened under fluid. The lower lobe of the right lung was firmly attached to the diaphragm by short multiple adhesions. Both lungs were markedly congested; when they were partly inflated and immersed, large emphysematous blebs were seen over the lower dorsal surface of the right lung. Others were seen over the lateral aspect of the apical and basal lobes. The diaphragmatic surface on both sides showed areas of petechial hæmorrhage. Diagnosis: interstitial emphysema.

Case 5, *male, age* 62 (*abdomen and chest bound*). The maximum intrapulmonary pressure reached was 189 mm. Hg after 9·8 litres of air had been injected (fig. 3). No air leaked through the water-traps from either pleural cavity. There was considerable interstitial emphysema in the neck. When the sternum was deflected, a fair amount of air escaped, but a large amount was trapped in the anterior mediastinum and associated loose connective tissues. Both lungs appeared to fill the thoracic cavity. A fairly large area of the right basal lobe was fixed by fine adhesions to the lateral chest wall. No adhesions were found on the left side. Both anterior surfaces of the lungs showed multiple emphysematous bullæ of various sizes (fig. 5) and the lungs looked considerably congested. When the lungs were examined under water no leakage of air occurred through either pleural surface. This again was a case of interstitial and subpleural emphysema.

The intratracheal pressure in the unbound corpse and in that with the abdominal binder only were much the same. On the other hand, in those cases where both the chest and abdomen were bound, the intratracheal pressures were very much higher, double in two cases. The type of injury observed in the unbound case was rupture of the lung and in the bound ones pulmonary interstitial emphysema.

Discussion

From the necropsy findings it is evident that in the unbound case rupture of the lung occurred at the site of the adhesions, which were basal; these were stretched, and shearing forces brought about the rupture. By providing support, the abdominal binder limited the downward expansion of the lungs, so that the basal adhesions were not able to stretch sufficiently to damage the visceral pleura. The lungs of this case, however, were unable to withstand pressures higher than those that cause pulmonary rupture in the unbound cadaver; interstitial emphysema developed at nearly the same intratracheal pressure. This was brought about by the rupture of the alveoli into the pulmonary interstitial planes, as the expansion of the chest was not limited by the tonus of the intercostal and other thoracic muscles. Our own experience shows that the safe intratracheal pressure is appreciably less when muscle relaxants are used in anæsthetised animals. Gerbode and Wright (unpublished) found that in anæsthetised dogs inflation of the lungs for 10 sec. to pressures ranging from 40 to 60 mm. Hg leads to gross interstitial emphysema, whereas in unanæsthetised dogs pulmonary barotrauma did not occur until intratracheal pressures of 60-100 mm. Hg were reached (Joannides and Tsoulos, 1930).

When both the abdomen and thorax were bound, higher pressures were tolerated before any evidence of lung damage appeared. None of these cases developed pneumothorax or rupture of the lungs, in spite of the presence of basal and other adhesions; all showed interstitial emphysema. It would thus appear that it is the over-expansion of the lungs that is responsible for pulmonary barotrauma; where adhesions are present, especially at the bases, rupture of the visceral pleura will occur with less distension. If the chest and abdomen are supported to prevent overstretching, pulmonary barotrauma is greatly diminished.

In living human beings it is likely that the comparatively strong rib cage plus muscle tonus will safeguard the middle and upper lobes, whereas the basal lobes require some form of diaphragmatic support such as could be provided by an abdominal binder. Malhotra and Wright (1959) found that in unanæsthetised rabbits the incidence of pulmonary barotrauma is very much reduced by the application of an abdominal binder alone.

The advanced age of most of the subjects available for this investigation no doubt accounts for the high incidence of pleural adhesions. The investigation does, however, provide an indication that the presence of pleural adhesions, especially at the base, predisposes to rupture of the visceral pleura and determines where it will occur. It would be useful to examine individuals who are likely to run the risk of pulmonary barotrauma radiologically to exclude the presence of pleural adhesions.

Summary

The intratracheal pressures at which pulmonary barotrauma occurs have been recorded in five cadavers, one unbound, one with abdominal binding and three with both chest and abdomen bound. Necropsy was done later to determine the site and nature of the injury.

In the unbound cadaver and in that with abdominal binding only, the pressures at which trauma occurred were approximately the same, i.e. 73 and 80 mm. Hg respectively. On the other hand, in those in which both chest and abdomen were bound, these pressures were very much higher, 190 mm. Hg in two cases and 133 in the third. In the unbound cadaver rupture of the visceral pleura occurred where basal pleural adhesions were present; in the remaining four, pulmonary interstitial emphysema developed.

When the intratracheal pressure is raised rupture of the lung is due to over-expansion; the presence of basal adhesions predisposes to this form of trauma. In cadavers, the abdominal binder protects against rupture of the basal part of the lung, but not against pulmonary interstitial emphysema; binding of both the chest and abdomen is, however, more effective.

The authors are most grateful to Professor Sir Roy Cameron for his guidance and to Sir Bentley Purchase for providing the facilities at St Pancras Coroner's Court for this work. They are also indebted to Professor K. Donald of the University of Edinburgh and Professor W. D. M. Paton of the University of Oxford for suggesting the problem, to Surg. Cdr T. W. Froggatt for information about the submarine disaster, to Dr S. L. Cowan for discussion and advice and to the Admiralty for permission to publish this paper.

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Volume 1, Number 3

July 1980

HOXRD6 1(3) 137–200 (1980)

ISSN 0195-9263

[redacted]

Hyperbaric Oxygen Review

PLENUM PRESS · NEW YORK AND LONDON

HBO Review, Vol. 1, No. 3

CEREBRAL GAS EMBOLISM (ARTERIAL) WITH SPECIAL REFERENCE TO IATROGENIC ACCIDENTS

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HISTORICAL

The first known recognition of arterial air embolism was by Morgagni. Personal observations and postmortem findings are recorded in his treatise *The Seats and Causes of Disease* published in English in 1769 (1). Actual occurrences undoubtedly go back to ancient times. A diving bell was reportedly used for salvage operations about 332 B.C., in the time of Alexander the Great (2). Surfacing from such an apparatus with breath holding in as little as six feet of water could lead to lung rupture, entry of air into pulmonary veins, and cerebral air embolism. Chest trauma, including penetrating and blast injuries, could have resulted in arterial gas embolism. In addition, it is possible to have gas embolism when there is a bleeding cavitary lesion in the lung and this must have been a risk factor especially in tuberculosis.

The modern era of high pressure work began in 1841 when Triger (3) used compressed air in a caisson for excavating the bed of the Loire River. Bert (4) in his great 1878 work, *Barometric Pressure, Researches and Experimental Physiology*, reports cerebral air embolism in dogs and describes its specific therapy: "When the decompression shows its effect by paraplegia, recompression must be carried out at once . . . for in this case we have to do . . . with some bubble of gas lodged in the vessels of the medulla, whose volume must be reduced at once so that the blood may drive it out." Since the 1920's, treatment

0195-9263/80/0700-0161$03.00/0

schedules have been developed by the U.S. Navy and in other countries (5-7). The recognition and treatment of cerebral gas embolism resulting from commercial pressure operations, military activities, especially training, and sport scuba diving, are well established on the basis of experimental studies and empiric observation (8).

Arterial air embolism may first have been produced iatrogenically when physicians began to irrigate empyema cavities. Roger, a French physician, is said to have been the first to call attention to these accidents in 1864, but they were generally thought to be of nervous origin and were called "pleural eclampsia" or "pleural epilepsy" (9). They became more frequent as the practice of puncturing cavities and carrying out artificial pneumothorax increased. An accident reported by Brandes (10) in 1912 was the first indication of the mechanism: in this instance bismuth paste was injected into an empyema cavity and the patient convulsed and died after 20 hours. Bismuth was found in the smallest vessels of the cerebral cortex of both hemispheres and serial sections from the wall of the sinus showed that the catheter had opened communications to pulmonary veins. Brauer (11), rejecting the theory of pleural reflexes, proposed that the accidents reported with increasing frequency represented air embolism, a theory substantiated clinically by Wever (12) in 1913 and confirmed by him with animal studies. Nevertheless, general acceptance of this etiology was delayed nearly 30 years (13, 14). Other causes of iatrogenic cerebral gas embolism will be discussed in the following sections. The recognition and, especially, treatment of iatrogenic cerebral gas embolism has lagged far behind medical knowledge and is not generally taught (15-17).

IMPORTANCE

Cerebral air embolism is the most serious type of decompression accident but the number of cases resulting from diving, etc. is difficult to ascertain because many of them are simply reported as drownings. Some idea of the frequency may be gained from the 1967 report of Smith (18). Over a 3 year period in Florida, 33 deaths were reported due to scuba diving, 42 were listed in Los Angeles in a 7 year period ending in 1960, and, in Seattle, 10 were ascribed to scuba in the 6 year period ending in 1965. The majority of these were probably air embolism deaths. About 70,000 dives per year are recorded by the United States Navy. Approximately two instances of cerebral air embolism occur per year and one, on the average, is a fatality (19, 20). Perhaps the best known air embolism accidents are those occurring during submarine escape ascent trainings (5, 20, 21). These are relatively few but occasionally result in mortality. Many minor cases are probably unrecognized. Air embolism was

detected by EEG changes in 4 of 112 submarine escape trainees in a report by Ingvan et al. (22) in 1973. Overall only 50% of patients with EEG changes developed clinical symptoms of neurologic damage.

Accidental (iatrogenic) arterial gas embolism is an under-recognized and under-treated grave complication of modern medicine. Instances resulting from diagnostic or therapeutic procedures in the chest were reported in the late 1900's and early part of this century. This subject was reviewed by Schlaepfer (9) in 1922 who included a number of reports of death and permanent neurologic damage. Arterial gas embolism has a wide variety of causes listed here in approximate order of importance: perfusion for heart surgery (23-28); heart procedures, especially on the left side or in the presence of septal defects (16, 29-32); intravenous therapy (33), especially with pressure injection (34-36) or in the presence of a patent foramen ovale etc. (37-40); placement (36, 41, 42) or use of central venous catheters that may inadvertently become disconnected; neurosurgery especially in the upright position (38, 43, 44, 46); diagnostic (9, 47, 48) or surgical procedures involving the lung (36, 49); surgery of the aorta or cervical arteries, head and neck procedures in surgery (50, 51); dialysis (36, 51-54), arterial catheterization especially arteriography (36, 55-57); abdominal or retroperitoneal gas insufflation (58); mechanical ventilation (59); uterine catheterization or insufflation (36, 52, 60) (usually criminal abortion and not medical); and liver transplantation (61).

Neurologic damage is recognized in a variable percentage of heart surgery patients but may occur in 5% or more. Heller et al. (62) reported a 9% incidence of organic brain syndrome after open heart surgery and 2% permanent neurologic deficits. Cerebral gas embolism is probably the most important cause and may occur as a result of air trapped in the heart or as an accident of perfusion. The astonishing frequency and severity of the latter is established by the recent report of Stoney et al. (23). In a retrospective survey of extracorporeal circulation for heart surgery in North America in the five year period, 1972-1977, there were 429 instances of arterial line air embolism with 92 deaths and 61 permanent neurologic injuries. The survey represents approximately 375,000 patients so the incidence of this accident is greater than one per thousand. The current incidence of damage from air trapped in the heart is not known but was formerly very frequent (31). The total occurrence of cerebral gas embolism probably greatly exceeds the figures reported by Stoney. To these numbers must be added all the other iatrogenic cases. Spencer (37) states "The danger of air embolism is frequently overlooked in cyanotic infants with right-to-left shunts, in whom air emboli can pass the heart and lungs and enter the cerebral or coronary circulation. With intravenous therapy much care is required to prevent small air emboli which almost routinely occur with the usual intra-

venous therapy during an operation." Gronert et al. (38) estimate that 20-35% of adult patients have a patent foramen ovale and that one in ten of these is at risk for cerebral air embolism when air inadvertently enters the venous circulation. They also estimate that venous air embolism occurs in 30-40% of neurosurgical cases done in the sitting position, giving a risk of perhaps one in 30 for these patients. In 1978, Peters and Armstrong (42) reported 14 cases of air embolism complicating central venous catheterization to show how easily this accident may happen. Four of their patients had transient central nervous system problems, and six of them died.

The mix of cases reaching hyperbaric facilities may be surmised from recent reports. Of 30 patients with cerebral air embolism reported by Hart (52) from California in 1974, 18 represented diving accidents, 11 were iatrogenic, and one was a criminal abortion attempt. One of the iatrogenic cases died (dialysis) as did the abortion case. Four patients had recognized permanent neurologic damage. Of 24 cases reported by Wattell et al. (36) from France in 1975, 13 were iatrogenic and 11 were postabortion cases. It appears likely that the major arterial gas embolism problem groups are sport scuba divers and medical accidents.

PATHOPHYSIOLOGY AND DIAGNOSIS

Mechanisms

There are three basic mechanisms of intraarterial gas embolization.

(a) Gas may be directly injected into an artery in the course of an extracorporeal perfusion (23, 25, 26, 31, 51, 63) or as a result of procedures such as arteriography (55-57).

(b) Gas may appear in systemic veins during decompression, be injected into veins during intravenous therapeutic or diagnostic procedures (33, 34, 42, 51, 54, 58), or be aspirated into veins during surgery and trauma, especially in the upper part of the body (43, 45, 46, 50). The passage of such gas into the left heart and arterial circulation may occur paradoxically in the presence of septal defects or pulmonary A-V fistulas (38-40, 61, 64-69) but lethal quantities can also pass through the pulmonary circulation in the absence of demonstrable abnormalities (53, 70, 71).

(c) Finally, gas may enter pulmonary veins or cardiac cavities during surgery (31), as a result of minor invasive diagnostic or therapeutic chest procedures (9, 47-49, 59), and as the result of trauma (9, 72-74). In diving the trauma is an increase in airway pressure due to breath holding or obstruction.

Immediate Effects

There is great variability in the manifestations of air embolism depending on the patient's position, the volume and type of gas, the size of the bubbles (75), and the rapidity of gas entry into the arteries, etc. (63, 76, 77). If the

patient is lying down, coronary artery embolism is most likely to occur (77, 78). Very small quantities of gas, as little as 0.5 ml, may produce dangerous or fatal cardiac arrythmias by blocking arteries and producing focal areas of ischemia (77). If the head is lowered, gas may be trapped in the left ventricle, a circumstance which may delay embolization (83). With the head up, or if the volume of gas is large, cerebral embolism and embolism to other organs may occur. In the brain, gas lodges in arteries, arresting blood flow and produces neuronal hypoxia and death.

The extreme variability of symptoms and signs is well described by many authors (53, 79, 80). When a significant coronary air embolism occurs together with cerebral gas embolism, the result is likely to be an early fatality which is frequently incorrectly ascribed to the cerebral embolism. Cerebral gas embolization should be assumed to have taken place whenever coronary gas embolism is identified. Unconsciousness or neurologic abnormality in a diver on surfacing is presumptive evidence of cerebral air embolism. Symptoms in the previously conscious subject, in descending frequency, are: dizziness, chest pain, paresthesias, convulsions, paralysis, nausea, visual disturbance and headache. Almost half of the patients will present unconscious or there will be a history of unconsciousness at some time. Additional patients will show altered consciousness. Neurologic patterns are quite variable. In the majority, symptoms and signs are ascribable to bilateral carotid and vertebral-basilar system dysfunctions. Isolated unilateral carotid or brain stem syndromes are less frequent. Signs and symptoms may change very rapidly. There may be sporadic or continued seizure activity. The presence of anesthesia or administration of analgesics or narcotics alters the presenting findings and may greatly complicate the evaluation. In addition to neurologic signs, there may be circulatory collapse, gross evidence of lung rupture, and a wide variety of pain syndromes.

The diagnosis should be entertained whenever there is a history of findings of central neurologic changes and the circumstances were such that a gas embolism could have occurred. In diving simple breath holding is all that is required. Absolute confirmation of the diagnosis is not always easy. Occasional patients will show air in retinal arteries, marbling of skin, irregular pallor of mucous membranes, or other pathognomonic signs (8, 9, 14, 15, 27).

Confirmation of a suspected diagnosis at surgery may be obtained by drawing arterial blood and demonstrating air bubbles. Inadvertent confirmation may occur when the aorta, coronary, or femoral artery is incised as part of the surgical procedure, revealing froth (24, 25). In nonoperative cases, appropriately placed incisions in the upper part of the body may show intravascular air bubbles (14) or they may be seen in fundal arteries. Arterial embolism during neurosurgery may be confirmed by detecting air bubbles in cerebral or cerebellar

arteries. In massive air embolization, air may be demonstrated in cerebral vessels by x-ray but this technique is unlikely to be useful except in postmortem examinations (14, 81). EEG changes are unlikely to be specific but will provide corroborative evidence of cerebral injury (82). Surviving patients may develop occult GI bleeding, presumably from embolic mucosal damage. In patients that die, careful autopsy procedures, including dissecting critical organs under water, may confirm the diagnosis (18).

Late Events

Gas bubbles may persist in the vertebral arteries and physically block blood flow for at least 48 hours (83). The vascular blockage produces cytotoxic cerebral edema because of the hypoxia. Endothelial edema or platelet thrombi may cause a "no reflow phenomenon" (84-87). In areas where circulation is reestablished it may be quite abnormal. There may be abnormal capillary permeability, small hemorrhages (88), and loss of vascular autoregulation. All of these processes may lead to what has been termed autodestruction (89). The net result may be infarction with demyelinization and death of neurons (89-91). The pathological changes following air embolization are thought to be more diffuse than those that follow other types of ischemia but are not pathognomonic (90).

From a practical standpoint what will happen to a patient is quite unpredictable. Unconscious patients and patients with severe neurologic impairment may make very rapid recovery, though in general, the greater the neurologic insult the longer the recovery. It is generally thought that patients who do not die tend to make full recovery after a prolonged interval (16). This is undoubtedly too optimistic a view. What probably happens in most instances is that patients learn to compensate for diffuse neuronal destruction and the abnormalities are manifested by minor things like changes in mood, effect or the like, which are not detected by the usual examinations.

PROPHYLAXIS

In diving, pulmonary conditions that may be associated with bronchial obstruction cause danger during ascent even when all usual precautions are taken (92). Such problems include pulmonary cysts, cavitary disease, bronchiectasis, chronic obstructive lung disease and acute pulmonary infection. Since venous air bubbles are to be expected in even the most careful decompression (93) and may cause paradoxical air embolism (39, 40), patients with cyanotic congenital heart disease (71), asymptomatic septal defects (38) and pulmonary A-V fistula should be excluded from diving. Starzl et al. (61) have reported probable cerebral air embolism from the graft in 9 of 48 patients after liver transplantation, presumably due to pulmonary arteriovenous fistulas associated with their chronic liver disease. Since individuals with cirrhosis of the liver may

have multiple small pulmonary arteriovenous fistulas, there may be more ready passage of venous air through the lung (67-69); cirrhotics should probably be excluded from diving. The potential seriousness of these various lesions serves to emphasize the need for a knowledgeable prediving medical examination. Careful training of divers is also essential. Inadvertent breath holding during ascent is very dangerous and, without training, is likely to occur when a diver runs out of gas or has some other problem that may affect his judgment and caution.

The problems of prophylaxis in medicine are formidable. It is extremely important to recognize the wide variety of risk situations and set up standard operating procedures even in the most routine circumstances, such as giving intravenous fluid (71). Because it is likely that medical personnel will continue to tolerate occasional or even frequent inadvertent air bubbles in intravenous administration, the routine use of a device to eliminate entrained air is indicated. This can be accomplished with a microporous membrane which will vent the air (Pall Biomedical Products Corporation, Glen Cove, New York). Such a device is probably mandatory for continuous intraarterial injections as for the treatment of head and neck cancer. Devices designed on the same principle may also be effective in preventing accidental arterial air embolization in open heart surgery and venous air embolization in dialysis.

The significant risk of air embolization with the insertion of central venous lines (42) makes it imperative that the patient be in head-down position or, preferably, on a positive pressure ventilator with continuous positive and expiratory pressure (PEEP) before venipuncture is undertaken. Absolute prevention of inadvertent disconnection is also important. The simple monitoring of the cervical or central veins by a doppler during neurosurgical (or similar) procedures in the upright or head elevated position is insufficient to prevent cerebral air embolization (38). The routine use of PEEP in the operating room would greatly reduce the risk of venous air aspiration in all types of surgery. In addition, the upright position should be avoided whenever possible.

The major problems of cerebral air embolization occur in conjunction with extracorporeal perfusion techniques for open heart surgery (23, 24). Blood damage, especially to platelets, makes it undesirable to use arterial filters. Disseminated intravascular coagulation is already a formidable risk with 472 cases and 163 deaths reported by Stoney et al. (23). Extracorporeal blood flows are high in relationship to reservoir volumes so that massive embolization can take place when the perfusionist's attention is distracted for a fraction of a minute. Low level reservoir alarms and arterial line alarms are available and probably should be utilized in all perfusions. In addition, the alarms should probably be backed up by automatic shut-off devices. It would be desirable to monitor the

bubble and particulate traffic in all perfusions but this is beyond the state of the art currently. These matters are discussed by Stoney et al. who, in addition, consider the desirability of more than one perfusionist in attendance (23). Study of these problems is currently being undertaken by the Utah Biomedical Test Laboratory under a Food and Drug Administration Contract. The scope of this study is detailed in a preliminary report (94).

Spencer (16) has stated "It is extraordinarily difficult to remove all intracardiac air . . . ." When precautions are not taken the air embolism rate is high. Nicks (31) reports 40 instances with 10 deaths in 340 cases prior to the institution of special precautions. Borik et al. (95) have recommended the use of a sterile ultrasound probe to detect the presence of intracardiac air prior to discontinuing bypass. Should air already be present in the aorta, Roe (96) has advised that intravascular carbon dioxide washout will prevent distant air embolism. Air may lodge in unlikely places, such as the leaflets of a prosthetic porcine heterograft. According to DeLaria et al. (97) properly placed traction sutures on the leaflets will make the valve incompetent and prevent air trapping. Others have suggested a variety of venting techniques (28, 98-100). On the basis of radiographic studies demonstrating that air may remain in the left ventricle for as long as one hour after it has resumed beating, Taber et al. (32) have advised a multiple aspiration procedure involving the superior pulmonary veins, the left atrial appendage, the left ventricular apex, and descending aorta while the heart is still fibrillating. Tsuji et al. (101) have advised the use of a ventricular-aortic probe that may be inserted through the ventricular apex; they used it in 2,500 cases but give no indication of the absolute benefits.

Even in the absence of any "accident" the extracorporeal circuit may be the source of gas emboli. Bethune (102) has emphasized the appearance of small bubbles during the priming procedure, especially when there is no blood in the prime. The best explanation for these bubbles is given by Galletti and Brecher (63) in their classic 1962 book *Heart-Lung Bypass*: "The formation of bubbles in the liquid is closely allied to the presence or absence of small invisible gas masses called gas nuclei. Gas nuclei are usually attached to hydrophobic areas or stabilized in surface cracks. They are also present on dust or particles suspended in the liquid. It is possible that multiplication and expansion of gas nuclei rather than supersaturation is the most important factor in bubble formation." That these bubbles appear quite commonly in freshly primed circuits should be strongly emphasized. It is common practice to remove bubbles by persistently tapping critical areas of the circuit and a bubble trap is quite helpful in their eventual elimination. Bethune advises flushing the circuit with carbon dioxide which is 20 times more soluble than oxygen and 100 times more soluble than nitrogen. A wide variety of circuit problems can cause the generation of gas

bubbles during the perfusion and must be guarded against diligently. These include aspiration of bubbles into any portion of the circuit where there is negative pressure, aspiration into some portions of the circuit where, even though the pressure may be positive, a Venturi effect causes a low pressure phenomenon, cracking of tubing in a pump head, inadvertent injection of air when a blood sample is taken, etc.

The use of arterial doppler monitoring of the cervical vessels may be useful (70, 103), and continuous EEG display, as practiced by many, is advisable.

EMERGENCY TREATMENT (*See also* ADJUNCTIVE THERAPY)

Emergency therapy is the subject of a recent communication by Fructus (104) who points out that it may be transiently effective and therefore has the danger that it may abort a recompression after diving accidents. The elements of emergency care for divers, which are applicable to many iatrogenic cases, include the following: 100% oxygen by well-fitting mask, a large single steroid dose, intravenous aspirin, and intravenous fluid such as Ringer's lactate and dextran (molecular weight 40,000). For the steroids, 1,000 mg of hydrocortisone or succinate, 30 mg of dexamethasone, or 160 mg of medrocortisone is advised. Intravenous aspirin is not available in the United States. Because aspirin may be life-saving as a result of its antagonism of platelet activation, oral aspirin should be given in its place when possible (105).

The method of transportation of patients is important, because, although speed is desirable, further decompression in an unpressurized plane cabin is very dangerous. For short distances, transportation on the ground or in a low flying helicopter is advisable. Long distance plane transportation should be in a pressurized cabin. A recent successful case was transported from Little Rock, Arkansas to Brook's Air Force Base in Texas at 8000 feet (49). The patient should be fully recumbent at all times or head slightly down, as gas may still be trapped in the left heart (78).

When gas embolism is suspected or occurs during open heart surgery, vigorous efforts should be made to clear all gross gas bubbles from the heart and aorta. If the patient is not hypothermic, he should be cooled, given 100% oxygen, a large single dose of steroids, intravenous aspirin, if available, should be administered, and the perfusion should be continued. It is generally a mistake to interrupt the surgery as the high oxygen tension, heparinization, and hypothermia tend to moderate the damage from the gas embolization (8, 23, 24).

Peirce (24) demonstrated the need to prepare for the risk of gas embolization during open heart surgery: "One should not assume that presently available

safety measures, such as low level alarms on reservoirs, pump shut offs and bubble detectors, important and promising as they are, will eliminate the risk of air embolism. . . . Teams engaged in open heart operations should familiarize themselves with the therapy of air embolism. They should ascertain the nearest location of a suitable hyperbaric chamber and, in conjunction with the chamber team, work out a detailed protocol to be followed in suspected, presumptive, or proved instances of air embolism." During the completion of the case, agreed on mechanisms should be activated so that, when indicated, hyperbaric therapy can be obtained with as little delay as possible. In this regard, Kindwall (8) has stated that transportation should be to a chamber capable of compression to 6 ATA no matter how distant. Conversely, Hart (52), who has had considerable experience with cerebral air embolism, has expressed the opinion that treatment at 3 ATA with oxygen may be superior. These opinions and the need to prepare for intensive supportive respiration etc. are matters that should be considered prior to the occurrence of air embolism cases by open heart teams. Probably most gas embolizations recognized during open heart surgery are salvageable.

Hyperbaric Therapy

Recompression is the specific recommended therapy for cerebral air embolization occurring during decompression (5-7, 19-22, 52, 57, 79, 80, 86, 106-115). It is also a specific therapy for other types of cerebral gas embolization including iatrogenic cases (8, 25, 26, 36, 49, 51-53, 55, 60, 80, 116-120). There is a considerable body of experimental work starting with Bert in 1868 (4, 5, 8, 89, 121-123). Efficacy results in the following: a) Compression of the gas bubbles which reduces their mechanical obstructive effect and hastens their reabsorption, b) exchange of oxygen for nitrogen when the bubbles are air and c) moderation of secondary phenomena including cerebral edema, disruption of microcirculatory flow, and increased intracranial pressure. Hyperbaric regimens attempt to provide optimal recompression combined with early use of oxygen. Recompression is most valuable when carried out immediately but may be life-saving for periods exceeding 24 hours. This may be because bubbles can remain in cerebral vessels for at least 48 hours (83) or because of the secondary effects of hyperbaria listed in *c* above. A list of hyperbaric chambers in the United States is given in the first issue of Hyperbaric Oxygen Review (124). Persons involved in any type of high pressure activity, open heart surgery, dialysis, etc. should familiarize themselves with the location of nearby chambers, facilities available, methods of transportation, and technique of referral.

Animal Research

Kent and Blades reported in 1942 (76) that 1 ml of air injected into a pulmonary vein of the dog was universally fatal due to coronary air embolus; 0.5 ml resulted in a 50% mortality and 0.25 ml was always tolerated. In the head-down position as much as 8 to 14 ml might be tolerated. In sharp contrast to the cardiac susceptibility to air embolism, they reported that 20 ml injected directly into a carotid was without demonstrable effect. They believed, therefore, that cerebral air embolism was of less importance than coronary air embolism. This, of course, is true for closed-chest dogs when resuscitative efforts are not made. It is not true for man who is frequently upright at the time of embolization and it is not true for open heart surgery where the heart is readily accessible and may easily be resuscitated. Smith et al. (121) reported in 1961 that dogs with simultaneous occlusion of both common carotid and vertebral arteries showed a loss of EEG activity in 80%. This change could be prevented if the occlusions were carried out at 2 ATA in oxygen. Fries et al. (83) demonstrated that the LD 50 of air injected into an internal carotid artery of the dog was 1 to 1.25 ml/kg and that 0.5 ml/kg produced permanent brain damage. They further showed that the LD 50 for oxygen was about twice as large and that the rapidity of injection of air or oxygen was not particularly important though their animals showed a large biologic variability. Their paper gives a good account of the types of neurologic damage occurring in animals. A very important observation at postmortem was that gas could be found in cerebral vessels of dogs who lived up to 48 hours after the gas injection. One ml followed by 0.5 ml/kg increments of air were injected into the left carotid of rabbits by Meijne and Boerema (2) until the EEG became flat or the blood pressure dropped to 50 mmHg or less. Animals with a blood pressure drop died unless they were compressed in oxygen to 3 ATA (66 feet or 25 meters of seawater). This also returned the EEG to normal. Iwa et al. (123) reported that 14 of 15 dogs receiving 1 ml/kg of air into the internal carotid died without compression treatment but that 80% receiving hyperbaric oxygen within 4 hours survived. The tolerance of arterial air embolism was shown to vary with the site of injection by Gómez et al. (77). The results of air embolism were less severe if the dogs were on cardiopulmonary bypass. Important observations were made by Waite and Mazzone (88) at the Naval Submarine Medical Center in 1967. Dogs were prepared with a calvarial window. Carotid injections of air produced visible bubbles and the cessation of local circulation. A maximum effect occurred between 1 and 2 ATA and there was evidence that all bubbles were removed and circulation restored by 4 ATA. Five of 6 dogs compressed to 6 ATA (165

feet or 50 meters seawater) for 10 minutes made a full recovery. The sixth had a cerebral hemorrhage. The authors believe that this circumstance may give insight into the failure of some persons to respond to recompression. Similar and more extensive work has been reported by Grulke and Hills (111).

The problems of reperfusion are the subject of many reports. There is a brief discussion under Pathophysiology but the full subject is beyond the scope of this review. A free blood-gas interface activates platelets and produces a form of disseminated intravascular coagulation. This may be one factor leading to a "no reflow" phenomenon and a failure to respond to recompression. The development of cerebral edema may also be important and delay any response to recompression. There is much evidence that hyperbaric oxygen is effective in combating both cytotoxic and vasogenic cerebral edema. The subject has recently been reviewed by Peirce and Jacobson (87). The beneficial effect of oxygen, even at normal pressure, was shown in animals by Fine and Fischmann in 1940 (125) though this result had been anticipated by Behnke et al. in 1936 (126). Relatively little research has been done on cerebral embolism in primates. Gosset et al. (110), using a monkey carotid embolism preparation, found that the maximum benefit was produced at 8 ATA in air for 30 minutes or 4 ATA for 2 to 3 hours. Their animals were followed with EEG's.

Development of Treatment Schedules

Until 1964 serious decompression sickness (Type II) was treated with Navy Air Tables 3 and 4, starting at 6 ATA (165 feet or 50 meters of seawater), which required 19 and 38 hours, respectively (6, 106). At that time Goodman and Workman (20), because of the high failure rate and prolonged time, modified the treatment schedule so that 6 ATA would be required only until the patient showed improvement. There was then rapid decompression to 2.8 ATA (60 feet) and oxygen and air were alternated (Table 5 or 6) to reduce the decompression time to between 2.5 and 5.5 hours. Bornmann (21) reported in 1967 that 123 cases of Type II decompression sickness showed an overall success rate of 93.5% when the new Early Oxygen Tables were used. He further reported full recovery in 12 buoyant ascent cases. One of these showed immediate relief at 60 feet and was not further compressed. Six cases showed complete relief after 6-30 minutes at 6 ATA. A more comprehensive report was given by Genderen and Waite (20) in 1968; that report includes notice of the approval of the new schedules by the Navy. At present, the only approved recompression schedule in the Navy (6) requires a uniform 30 minutes at 6 ATA (Table 6a) but provides considerable latitude in the use of alternating oxygen and air after rapid decompression to 2.8 ATA (19).

The letter designation in Table 6a refers to a schedule that includes the original compression, 30 minutes at 6 ATA, and the decompression to 2.8 ATA. Without the letter Tables 5 and 6 include only that portion of the schedule at 2.8 ATA and below. Table 5 has a shorter schedule than 6. Both may be used with extensions (additional time) at 2.8 or 1.4 ATA. ATA means atmospheres absolute. A graphic conversion of units is shown by Peirce (127).

In a recent workshop, Berghage et al. (106) review the history of the U.S. Navy diving tables and show how the early oxygen regimes were worked out with the help of only 33 experimental subjects. Some of the earlier Navy tables were based on as few as 6 subjects.

There are various options when the patient fails to respond at 6 ATA (19, 108). These include: a) remaining at 6 ATA for 2 hours and then decompressing on Air Table 4 to 2.8 ATA followed by the Air-Oxygen Table 6, and b) change to nitrogen-oxygen saturation therapy at 4 ATA as advocated by Miller et al. (113) in 1978. These options may also be used for recurrence at 2.8 ATA. The schedule used by the Royal Navy is somewhat different and is reported by Leitch (7). Civilian use of the new Table 6a was reported for cerebral air embolism by Kindwall (8) in 1976. Three post scuba and one open heart case survived. A patient who received a 50 ml air injection, instead of contrast material, into the aortic arch died.

Some large civilian chambers do not have the capability of compression beyond 3 ATA though most facilities have supplementary capability to 6 ATA. There are, in addition, many hyperbaric installations using monoplace oxygen chambers that are capable of use only to 3 ATA. Hart (52) in 1974 reported successful use of 3 ATA with oxygen in the treatment of patients with cerebral air embolism. He also reported experience using 6 ATA and the longer Navy Table 6a but stated that his results at 3 ATA with oxygen were superior. In the monoplace chamber it is not possible to alternate air and oxygen to moderate cerebral oxygen toxicity and limit the possibility of convulsions. For this reason the recommended schedule is 3 ATA for 30 minutes followed by 2.5 ATA for 60 minutes with repeated treatments as indicated. Wattel et al. (36) have also reported successful use of oxygen in a monoplace chamber at a pressure of 2.1 ATA. Further detailed investigation is required to determine the relative efficacy of early oxygen of 2.8 ATA versus greater compression to 6 ATA in air. The weight of current evidence would suggest that the preferable treatment is an initial period at 6 ATA in air followed by rapid decompression and the use of alternating air and oxygen.

Clinical Experience

Much of the more pertinent diving experience has been covered above under the development of tables. Most deaths occur early, perhaps as the result of cardiac arrhythmia or circulatory failure (76). Deaths at the treatment facility generally are in subjects that do not respond to therapy. They tend to be those that arrive after long delays and have maximal neurologic damage. Gillen (79) reported an 8% mortality in 79 patients, including 4 patients who were dead before recompression, 2 who were probably dead before the start, and 3 who received no benefit of treatment. Davis (107) reported 4 deaths in 25 cerebral embolism cases treated in Air Force chambers. Only 3 were received with delays less than 2 hours. The mortality would, therefore, appear to be low in patients arriving at a hyperbaric facility alive. Polland et al. (114) reported a graver prognosis in patients with both cerebral and cord involvement. Hart (52) reported that 9 of 18 patients became asymptomatic after the first treatment; 4 of the remaining 9 had permanent neurologic residuals.

The data of Stoney et al. (23) supports the hypothesis that clinical reports of cerebral embolism after open heart surgery cover only a small fraction of the total cases. The mortality in the full group is high. In the 429 arterial line air embolism cases reported by Stoney, there were 92 deaths (21%) and 61 permanent injuries (14%). A 1967 report by Nicks (31), covering the problems of intracardiac air in 340 patients, gives 10 deaths in 40 cases (25%). A single patient reported by Menkin and Schwartzman (27) in 1977 was in a vegetative state 43 days after an arterial line accident. Stoney includes the case report of a patient dying in coma one week after massive cerebral air embolism and one case, not elsewhere reported, is in the communication from Peirce (24).

In reviewing the literature one is struck by the absence of any mention of hyperbaric therapy for cerebral gas embolization in texts discussing complications of open heart surgery (16, 17). Wattel et al. (36) report two post-open heart cases treated with hyperbaria but do not state whether they survived. In all, they report survival of 21 of 24 iatrogenic cases treated, including two post open heart. A Russian report by Bourakovsky and Bockeria (116) indicates deaths in 5 of 7 patients treated hyperbarically 4-36 hours after air embolism occurred during open heart procedures. Six patients reported in five additional communications survived following hyperbaric oxygen therapy despite the gravity of their neurologic problems (25, 26, 52, 117, 118). Patients with cerebral emboli occurring during open heart surgery that did not receive hyperbaric therapy had a lower survival than patients with decompression air embolism who were treated hyperbarically. The heart cases had a 21% mortality compared to a mortality of 0-8% in the diving group. Numerous authors have

pointed out that heparinization of the patient, concomitant use of hypothermia and maintenance of the circulation by perfusion should improve the prognosis relative to diving accidents. That the figures do not bear this out may be a reflection of the severity of the cases and the infrequency with which hyperbaric oxygen is used in post-open heart accidents. Nevertheless, the results of hyperbaric therapy in the post-open heart patients is very promising. Reported patients have survived despite delays of up to at least 24 hours (117).

There are a wide variety of other iatrogenic types of gas embolization that have been treated by hyperbaria but the numbers are small. Results have generally been favorable when the patient was not in extremis and the time delay was not excessive. There are several reports of successful therapy of cerebral air embolism occurring during renal dialysis including a Japanese report (51, 53). Hart (52) reports one death in a patient with massive embolization despite hyperbaric therapy. The use of alarms and shut off devices, combined with suitable filter vents, should essentially eliminate this type of problem but, when it occurs, hyperbaric oxygen would appear to be the treatment of choice. At least one postarteriographic case has been successfully treated (55) but Kindwall (25) has reported a failure where air was injected instead of contrast material into the aorta for an arch study. Other successfully treated cases include those arising from lung biopsy (49), during cardiac catheterization (55), pleural puncture (36), and subclavian catheterization (55). One of four abortion cases reported by Rapin et al. (60) died and two had major residuals despite hyperbaric therapy. Success has occurred after delay periods of as long as 48 hours, which is encouraging (49).

ADJUNCTIVE THERAPY

This subject has recently been discussed by Kindwall (105). Steroids do not appear to increase central nervous system toxicity during hyperbaric oxygen treatment. They should be given as a single large dose (104) or for no more than 72 hours. Aspirin is useful and may be given early or even as a prophylactic medication. Administered orally, the maximum effect is in approximately 30 minutes. Heparin is contraindicated in vestibular decompression sickness and may be contraindicated in air embolism as shown by one instance of hemorrhage in the small experimental series of Waite and Mazzone (88). Kindwall recommends 50% glycerol orally for cerebral edema. This is said not to cause rebound edema. A dose of 0.8 ml/kg has its maximum effect in one hour and a duration of action of 6 hours. For shock, dextran (MW 40,000 followed by MW 70,000), plasma, or plasmanate etc. are advised. Digitalis is useful if the heart rate is high despite adequate fluid supplementation. Opiates are generally contraindicated

because they may mask symptoms and hinder evaluation of the patient's response to treatment. Convulsions are best treated with diazepam given intravenously in 10 mg doses as required. This drug may also be used as a sedative. Water or 5% dextrose in water should not be used because they may aggravate cerebral edema.

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Mechanisms in Development of Interstitial Emphysema and Air Embolism on Decompression From Depth

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ABSTRACT

SCHAEFER, KARL E., WILBUR P. MCNULTY, JR., CHARLES CAREY AND AVERILL A. LIEBOW. *Mechanisms in development of interstitial emphysema and air embolism on decompression from depth.* J. Appl. Physiol. 13(1): 15–29. 1958.—Unprotected dogs decompressed from 100- or 200-foot equivalent depth (water) with trachea closed developed pulmonary interstitial emphysema and air embolism, probably via the pulmonary veins, when the intratracheal pressure reached a critical level of approximately 80 mm Hg. The lungs became markedly distended by entrapped air expanding as the ambient pressure was reduced. The systemic aortic pressure fell in consequence of compression of postarterial vessels in the lungs, indicated by a higher gradient between pulmonary arterial and left atrial pressures. Interstitial emphysema and air embolism could be prevented by the application of thoraco-abdominal binders, despite a rise in intratracheal pressure to levels of 180 mm Hg or more. The effects of the binders were: *a*) to prevent overdistention of the lung as indicated by the small difference between the intratracheal and intrapleural pressures; *b*) to keep at a lower level the pressure gradient between the respiratory passages and the pulmonary veins—left atrium; *c*) to maintain the systemic aortic pressure, in part, at least, in consequence of a low transcapillary pressure gradient. These observations suggest the possible utility of compressive garments of the 'G-suit' type in escape procedures. The critical factor for the development of pulmonary interstitial emphysema and air embolism appears to be not an absolute level of the intratracheal pressure, but rather a transpulmonic pressure in excess of 60–70 mm Hg or a transatrial pressure in excess of 55–65 mm Hg.

INTERSTITIAL emphysema and air embolism are recognized hazards of decompression from high pressure. Both have occurred as accidents in diving and submarine escape training (1) and may also account for low survival rates in genuine escapes from submarines (2).

Air embolism is to be distinguished from decompression sickness, or caisson disease. In the former, the exposure to high pressures is usually insufficiently long for appreciable solution of gases in the blood and tissues. Air is presumed to enter through some break in the continuity of the vascular system. The confusion that at first existed between decompression sickness and air embolism as the mechanism of serious symptoms (3, 4) or even death (5), after ascent from depth, has gradually been resolved.

In order to reduce the dangers of air embolism during escape training, men have been taught one of several methods: *a*) to maintain ventilation into an escape apparatus, such as the 'Momsen lung', *b*) to exhale during free ascent, or *c*) to exhale completely before the ascent and continue to exhale as volume of air in lungs increased during ascent. Otherwise, with ascent, the expanding air confined within the lung might tear the tissue and gain entrance into delicate vessels. Such entrapment could

Received for publication November 12, 1957.
[1] In contract with the Office of Naval Research.

occur if an individual, in panic, kept his glottis closed or if local pathology prevented free venting of some segment of the lungs.

In spite of precautions, several instances of fatal air embolism have occurred recently as a result of submarine escape training (6). In each instance a normal ascent had been made. There was no indication that these men had held their breath. There was, nevertheless, evidence of air embolism at necropsy.

That fall in systemic arterial pressures with its consequences might also have been important in the mechanism of death under circumstances of increased pressure in the airway finds some support in experiments by Bjurstedt and others (7–9). They interpreted the systemic hypotension to reflect a decreased circulating blood volume, resulting from pooling in the abdominal viscera as a consequence of the greatly increased intrathoracic pressure. Systemic hypotension and even total abolition of arterial pulsations indicating cessation of blood flow had been observed as early as 1920 by Chillingworth and Hopkins (10), who placed their animals in a vacuum chamber except for an outlet into the trachea. Evidence suggesting reflex effects of explosive decompression, with cardiac slowing and hypotension, was presented by Whitehorn and his collaborators (11).

In the pioneer experiments of Polak and Adams (12), it was determined that air embolism would occur in dogs at an intratracheal pressure of approximately 80 mm mercury and that air embolism could be prevented by controlling distention of the abdomen and thorax by means of binders. The beneficial effect of binders could be ascribed to the prevention of pulmonary distention, but possibly also to effects upon the circulation.

The present investigation was undertaken *1*) to determine the effects upon intratracheal, intrapleural and, in some instances, intra-abdominal pressures and pressures in various parts of the circulation, of decompression from depth with the airway open and with the airway closed; *2*) to establish more exactly the values of the parameters that determine the occurrence of air embolism; *3*) to evaluate the possible role of the circulatory effects in the mechanism of death and *4*) to determine the effects of binding the abdomen or thorax, or both, upon these various pressures, and to evaluate the effects of such procedures upon mortality.

Three series of experiments were performed, but these could be subdivided into two parts. In PART I, a series of dogs was decompressed from a simulated depth of 100 feet, while intravascular and certain intracavitary pressures were measured. In another series, the procedure was identical, but decompression was from 200 feet. In both series abdominal and chest binders were used in several cases. In PART II, the experiment was simplified inasmuch as intravascular pressures were not measured, but the design was simply to test the effects of binders upon survival in correlation with intratracheal pressure.

PART III of this report deals with observations at necropsy in animals studied physiologically in PART I.

METHODS

Equipment for Compression and Decompression. The no. 2 compression chamber at the New London Submarine Base was used to accommodate the experimental animal and appropriate parts of the recording equipment. This chamber can be compressed to simulated levels of 100 feet within 2½ minutes and decompressed to sea level from this depth in approximately 1 minute. Compression to 200 feet occupies 4 minutes and decompression takes place in approximately 1½ minutes. The animals were kept for 1 minute at the 100 or 200-foot pressure.

Preparation of Animals. Dogs for the first part of the experiment were prepared 2–4 weeks prior to study by thoracotomy to enable the suturing of polyethylene plastic guides to the pulmonary artery and aorta. The manner of their application and use has been previously described (13). These guides provided access to the vascular compartments with the necessary airtight closure.

Procedure During Experiment. Animals fasted overnight were anesthetized with pentobarbital sodium intravenously in doses of 35 mg/kg. The tracheotomy was done through as small an incision as possible and a glass T-tube was inserted and tied firmly into the trachea so as to prevent leakage. A side branch of the T-tube was used for the electronic recording

of pressure and the free end was provided with a valve that could be closed at will. In PART I, a solenoid valve of ½-inch port controlled from outside the chamber was used for closure. Valves of this type with large lumens were, however, found to exhibit a tendency to leak. For this reason, a scissors type of clamp was used in PART II.

Cardiac and vascular cannulations for electromanometry were performed by making minute skin incisions over the previously implanted needle guides and introducing a Gauer manometer[2] through each, directly into the lumens of the pulmonary artery and left atrium, with their pressure-sensitive tips just inside the respective vascular compartments. The skin wounds were approximated by ligature about the manometers to provide an airtight seal. The femoral arteries and veins were cannulated to give access to the inferior vena cava and aorta. Either Gauer manometers were used directly or P.E. 50 plastic cannulas were employed in connection with strain gauges. The plastic cannulas had a length of 12–15 inches and the strain gauges to which they were connected were placed as close as possible to the body of the animal. Various combinations of these recording procedures were employed. Polyethylene cannulas, in some instances provided with saline-filled balloons, were introduced into the abdominal and pleural cavities, with precautions to avoid pneumothorax, and the skin wounds were again made airtight. Pressure recordings were made with the Sanborn Polyviso and two Brush recorders.

Following heparinization (4–5 mg/kg), bubble traps were introduced into the carotid arteries and external jugular vein in such a way that blood traversing these vessels had to pass through the trap. These traps were glass and plastic modifications of the device used by van Allen and Hrdina (14). Gas bubbles in the blood would be caught at the top of the purposely expanded trap, where flow was turbulent.

Binders. For certain of the animals, binders were applied. Three-inch adhesive tape was unrolled, then loosely rerolled in order to avoid excessive tension during application. The animal was suspended supine upon supports and the tape was applied, not too firmly, to follow the contours of the body and in such a manner that there was no restriction of ordinary breathing movements. The binding was confined to the abdomen in some experiments, but in others it was carried upward over the thorax.

Following these preparations for PART I of the experiment, the dogs were placed in the pressure chamber and the various connections for electromanometry and for closure of the tracheal valve were made. The oscillators and preamplifiers for the Gauer manometers and the power supplies for the strain gauges were located in the pressure chamber. The outputs were led out through a cable to the Sanborn or Brush direct-writing oscillographs.

For PART II of the experiments, the dogs were decompressed in pairs, one with unsupported chest and one with thoraco-abdominal binder. The tracheal cannula was inserted and the pressures within the airway were measured as before, but closure during 'ascent' was accomplished by means of a scissors clamp. This clamp was caused to compress a segment of rubber tubing by energizing a solenoid valve from outside the chamber.

Necropsy Procedure. Many of the necropsies were performed with the animals submerged in water, beginning with the skin incision, according to the recommendations of Köhn (15). That this procedure is ordinarily necessary for the proper interpretation of the presence of intravascular gas bubbles was demonstrated in one instance where no air was found in the cranial cavity when opened under water. After the head was momentarily lifted from the water and submerged again, the cortical veins were seen to contain many bubbles. The presence of gas bubbles in the carotid and jugular bubble traps, however, was in itself evidence of air embolism. In most experiments in which there was manifest evidence of air embolism through the presence of gas bubbles in the bubble traps, autopsies were conducted without a water seal.

OBSERVATIONS. PART I

Intracavitary and Intravascular Pressures in Animals Decompressed From Depth. Observations made upon animals compressed to 100

[2] A variable inductance device for determining pressures within a vessel or chamber without intervening fluid column.

and 200-foot depths may be grouped together, since the compression is simply a means of obtaining a high intratracheal pressure and the attempt is to relate this to other pressures. Moreover, incompetence of the solenoid valve in some of these experiments influenced the maximal intratracheal pressure attained, as did the phase in the respiratory cycle at the moment of interruption of the airway. These variations in intratracheal pressure could be accurately recorded and were actually desirable, since the variations in the values of the parameters thus induced could be correlated with development or absence of damage to the lung and of air embolism. It should be mentioned that no signs of incompetence of the scissors clamp used for interrupting the airway were observed in the simplified experiments of PART II, in which only intratracheal pressures were recorded. There was probably also less leakage than in the first two series of experiments where some air probably escaped from the body along the many catheters and cannulas that penetrated the skin.

Animals compressed and decompressed with open airway showed no appreciable changes from control values obtained prior to compression, in intracavitary or intravascular pressures in relation to ambient pressures. After a series of preliminary trials, with intermittent closure and opening of the trachea in various patterns, it was decided to simplify the procedure by keeping the trachea closed during the entire ascent. Most of the animals in the experiments of PART I were subjected to repeated ascents under various conditions, sometimes as many as seven, concluding with the most stressful and likely to terminate in air embolism. It therefore became necessary to record the observations according to the number of ascents as well as animals, as in table 1. In each experiment a control run was made during which the animal was compressed and decompressed with open airway.

Groups A and B. If the trachea was kept closed throughout the ascent, the data could be subdivided into two groups. *Group A* comprises observations upon animals which developed air embolism or extensive interstitial pulmonary emphysema. All but one of the seven animals in *group A* had air embolism and the last had extensive interstitial emphysema of the lungs and mediastinum. *Group B* consists of observations in instances where fatal air embolism was not observed. Some of these were collected during earlier 'ascents' with animals that succumbed to air embolism in a subsequent ascent, from which recorded data

TABLE 1. CONTROL AND PEAK PRESSURES IN DOGS DURING 'ASCENTS' FROM 100 OR 200 FEET EQUIVALENT DEPTH WITH TRACHEA CLOSED

		Group A			Group B			Group C			Group D		
		Mean	N	As	Mean	N	As	Mean	N	As	Mean	N	As
Intratracheal	Start	1.9±4.2	7	8	2.0±5.1	5	9	5.0	2	2	3.6	2	8
	Peak	88.6±15.5	7	8	59.0±9.8	5	9	130.0	2	2	82.1	2	8
Intrapleural	Start	−3.0±3.9	4	5	−6.3±2.5	3	5	−4.0	2	2	−4.2	2	8
	Peak	9.4±5.6	4	5	7.9±6.8	3	5	31.0	2	2	55.4	2	8
Intra-abdominal	Start	−1.5±4.3	4	4	0.92±2.1	4	6	5.0	1	1	4.2	2	8
	Peak	18.8±5.6	4	4	11.8±9.3	4	6	30.0	1	1	42.0	2	8
Pulmonary arterial	Start	9.8±10.8	6	7	3.8±6.9	4	8	13.0	2	2	8.2	2	8
	Peak	54.9±11.9	6	7	27.2±3.2	4	8	55.0	2	2	68.5	2	8
Left atrial	Start	1.7±7.6	6	7	−5.3±3.1	4	6	−3.0	2	2	2.4	2	8
	Peak	19.8±9.5	6	7	13.8±4.2	4	6	36.0	2	2	56.1	2	8
Systemic arterial	Start	103.2±11.6	7	8	90.7±15.9	5	9	97.5	2	2	125.4	2	8
	Peak	22.8±9.0	7	8	36.0±17.2	5	9	43.0	2	2	104.1	2	8
Systemic venous	Start	1.1±5.2	5	6	−1.9±2.1	5	9	9.5	2	2	5.4	2	8
	Peak	17.1±12.9	5	6	18.7±7.5	5	9	30.0	2	2	71.8	2	8

Group A, animals without binders that developed air embolism. *B*, animals without binders that did not develop air embolism. *C*, animals with abdominal binders (both developed air embolism). *D*, animals with thoraco-abdominal binders (neither developed air embolism). N = no. of animals. As = no. of ascents.

Figures represent pressures in mm Hg, with their standard deviations, based on means weighted by the number of ascents for N animals.

are included with *group A*. It is possible that interstitial emphysema may have developed during earlier runs, but the bubble traps yielded no evidence of air embolism until the final ascent.

A comparison of *groups A* and *B* is useful in beginning an analysis of factors that determine air embolism (table 1). The peak intratracheal pressures were significantly higher ($P < .01$) when air embolism developed (*group A*) while the intrapleural and left atrial pressures were not strikingly different in the two groups.

Of particular interest is the difference between the intratracheal and intrapleural pressure, which has been called the transpulmonic, transthoracic or transmural (7–9) pressure. This serves to relate the intratracheal pressure to the degree of distention in the lung. Thus, if for a given intratracheal pressure, the intrapleural pressure is relatively low (transpulmonic pressure high) the indications are that the lung is unduly distended; conversely, any means for elevating the intrapleural pressure for a given intratracheal pressure will result in a low transpulmonic pressure. Even more significant may be a concept of 'transatrial' pressure, the difference between the intratracheal and intra-atrial pressure. This would indicate a gradient of pressure between the alveoli and the atrial chamber and, therefore, the force potentially impelling penetration of intra-alveolar gases into the pulmonary venules and left heart. The transatrial pressure is probably the more fundamental datum with regard to the development of air embolism and was, therefore, determined in the course of the present experiments. Actually, since intra-atrial and intrapleural pressures ran rather closely parallel, transatrial was observed to pursue the same relative course as the transpulmonic pressure under all circumstances studied (fig. 1). In practice, the transpulmonic pressure is much more easily measured and is further considered below.

Both the transpulmonic and transatrial pressures are high in animals of *group A* (tables 1 and 2). The average value of the peak transpulmonic pressure which resulted in air embolism or emphysema was 68 mm of mercury with a range of from 62 to 85 mm of mercury. The use of decimal fractions in the table should not be taken to imply a degree of accuracy better than indicated by the nearest whole digit.

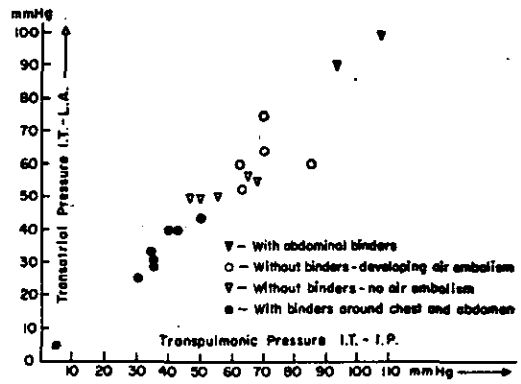

FIG. 1. Relationship of transthoracic and transatrial pressures. These fall along a straight line (peak pressures). Transatrial pressure (intra tracheal, I.T.—left atrium pressure, L.A.) vs. transpulmonic pressure (intra tracheal, I.T.—intra pleural pressure, I.P.).

There was little difference in the maximal levels of intra-abdominal and systemic venous pressure at the end in the two groups. The peak pulmonary artery pressure was higher, and the systemic arterial pressure fell more in the group in which air embolism developed.

The circulatory events leading to air embolism in a dog decompressed from 200 feet are illustrated in figure 2. In this record, the intratracheal pressure was plotted from another record made with the Brush recorder, while the other four are reproductions of the original Sanborn polyviso record. In this instance, the arterial pressure was relatively low at the start, but this was the 6th 'ascent' to which the animal had been subjected and the anesthesia had been prolonged.

At a depth corresponding to approximately 30 feet, the pressures in the pulmonary artery and venous pressure reached a peak which was preceded by two dips reflecting respiratory efforts. It is noteworthy that, at this point, all circulatory pressures appeared to have approximately the same value of 50 mm mercury and that cardiac action had practically stopped and pulses were eliminated from the records. At this moment the left and right heart had about the same pressure and, since the vena caval pressure was not different from intrapleural and intra-abdominal pressures (the latter was measured, but is not displayed in this record), one can assume that an equalization of pres-

TABLE 2. EFFECTS OF DECOMPRESSION FROM DEPTH WITH TRACHEA CLOSED: MAXIMUM GRADIENTS ATTAINED

Gradient	Group A			Group B			Group C			Group D		
	Mean	N	As	Mean	N	As	Mean	N	As	Mean	N	As
Transpulmonary (I.T.–I.P.)	68.1±6.3	4	5	54.2±6.0	3	5	99.0	2	2	29.2	2	8
Transatrial (I.T.–L.A.)	63.6±8.0	5	7	43.3±12.5	4	6	94.0	2	2	26.0	2	8
Transcapillary (P.A.–L.A.)	31.2±12.8	5	6	13.7±3.3	3	5	19.0	2	2	12.5	2	8

I.T. = intratracheal; I.P. = intrapleural; L.A. = left atrial; P.A. = pulmonary arterial.

The difference between transpulmonary pressures for *groups A* and *B* is statistically significant ($P < 0.01$ when determined by means of Fisher's '*t*' factor); likewise for difference between transatrial pressures.

N = no. of animals and As = no. of ascents, are not the same as in table 1 since a complete set of data could not be obtained in all animals.

sures within the circulatory system and the surrounding tissues had developed.

Immediately thereafter, there was a pressure drop in the pulmonary artery, left atrium and vena cava which might indicate a change in the tonus of vessels, although this point was not established. At approximately 10 feet of depth, pulses reappeared in the record of the circulatory pressures simultaneously with a drop in the intratracheal pressure. This would appear to be the moment at which air embolism occurred. After reaching the surface and opening the valve, the vena caval pulse pressure immediately reached about 40 mm Hg, compared with 5 mm Hg at the beginning of the ascent. There was a high pulse pressure in the cava suggesting tricuspid insufficiency, associated with distention of the right heart. Venous return was probably also augmented. The pulmonary artery and left atrial pulse pressures rose, but somewhat later, and to a much lesser degree than in the case of the vena cava. These pressures never reached the initial value prior to ascent. Finally, the pulse pressure in the systemic artery increased, although the diastolic pressure remained very low, at about 10 mm Hg (systolic pressure = 90 mm Hg). The mean pressures recorded from the venous system and the pulmonary circulation remained elevated, in comparison with initial values, in part probably because no respiratory efforts were made by the animal after the surface had been reached. The records show, quite a few seconds later, signs of a failing heart. One hundred and twenty seconds after reaching the surface, the chamber was entered and bubbles were observed in the carotid artery trap, while the trap for the jugular vein did not show any bubbles.

Figure 3 illustrates an experiment in which rather high intratracheal pressures were reached without the development of air embolism. The circulatory pressures, with the exception of the systemic arterial pressure, rose to a peak value, but at between 30 and 20 feet depth they fell at a time when the intratracheal pressure was still rising, as in figure 2. The pulses in the left atrium and pulmonary artery tracings did not disappear in this instance.

The fluctuations in the intratracheal pressure recording which occurred between 20 and 10 feet were reflected in all other circulatory pressure recordings and in the intrapleural pressure. The meaning of these changes is not clear. Upon reaching the surface and opening the tracheal valve, pulmonary artery and atrial pressure at once showed a large overshoot. It took 25 seconds until the systemic arterial pressure reached the highest values. The left atrial pressure rose to the peak value at about 10 seconds after the opening of the valve and the vena cava showed only minor changes in the range of normal. This seems to indicate that, with a less reduced blood flow during decompression (as compared with fig. 2), a more limited amount of accumulated blood started to flow again. There was no sign of tricuspid insufficiency.

Groups C and D. The effects of abdominal (*group C*) and thoraco-abdominal (*group D*) binders during decompression from depth are recorded in tables 1 and 2. Complete studies are available only in two animals from each group, although a number of ascents were studied for *group D*. Under both circumstances, the intratracheal pressures reached very high levels.

In figure 4 are shown graphically the effects

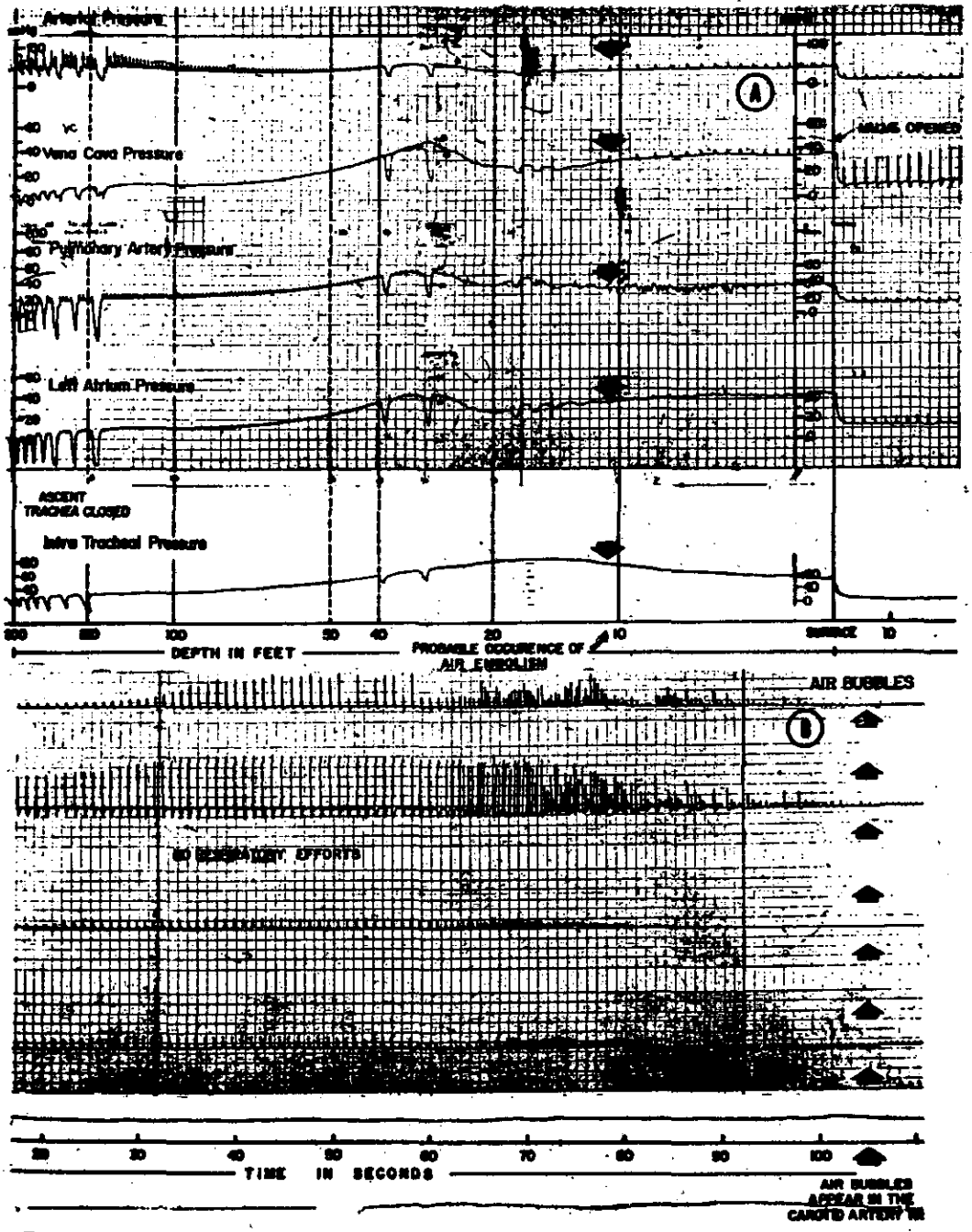

FIG. 2. *Exp. 23* showing development of fatal air embolism. Intracavitary and intravascular pressures in dog decompressed from 200-ft. equivalent depth who died of air embolism. Record *2A* continuous with *2B*.

upon the various pressures of an ascent from a 100-foot depth with trachea closed, with binders off (lower half) and with binders on (upper half). It is obvious that the binders resulted in a high rise of intrapleural, intra-atrial, pulmonary arterial, left atrial and systemic venous pressures roughly parallel to the rise of intratracheal pressure, while without

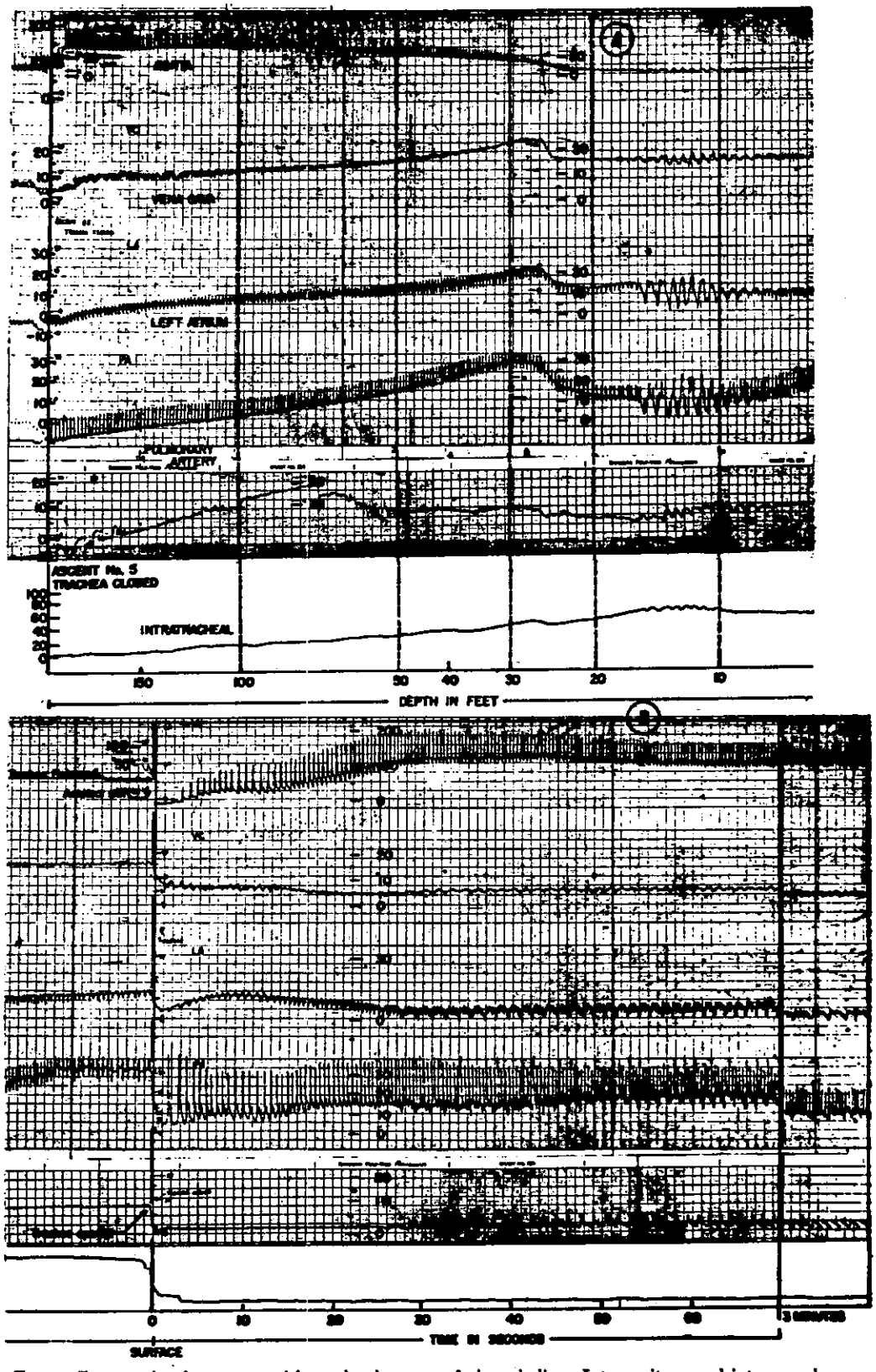

FIG. 3. *Exp. 20* showing ascent without development of air embolism. Intracavitary and intravascular pressures in dog decompressed from 200-ft. equivalent depth who survived this ascent. Record 3*A* continuous with 3*B*. (Tracings of figs. 2*A* and *B* and 3*A* and *B* have been darkened in order to be sufficiently visible in publication.)

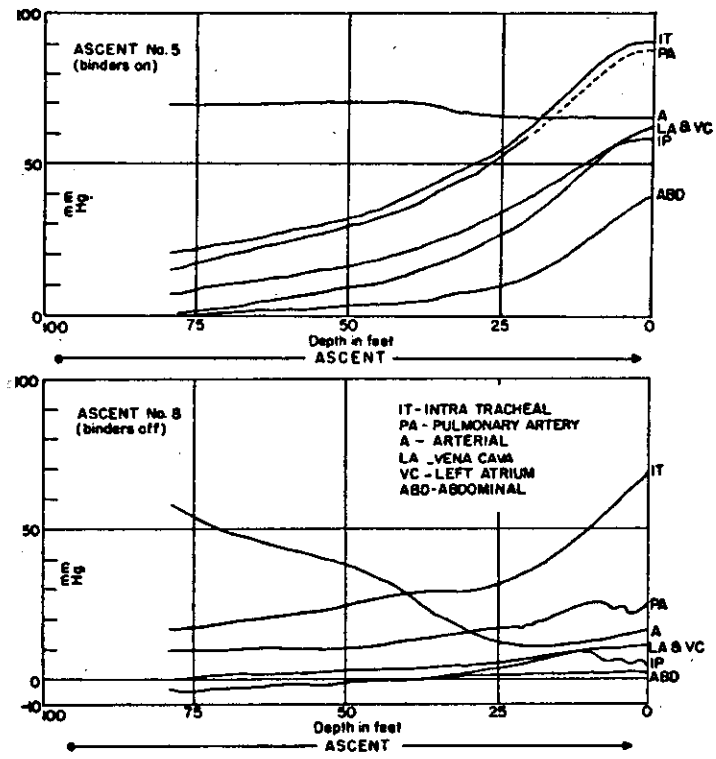

FIG. 4. *Exp. 13* showing thoracic and circulatory pressures in dog during 2 ascents (decompression from 100-ft. equivalent depth) with and without binder around chest and abdomen.

the binders the only notable rise occurred in the intratracheal pressure. Without the binders, systemic arterial pressure fell perceptibly. When the binders were on, this pressure fell very slightly.

The transpulmonic and transatrial pressures were much higher in the animals that had only abdominal binders (*group C*). In this group, transpleural pressures were in excess of 90 mm Hg and interstitial emphysema and air embolism developed, as is to be expected in animals with transpleural pressures in excess of the threshold, as established above. It is evident that abdominal binders alone did not prevent distention of the chest. On the contrary, when both thorax and abdomen were supported by adhesive tape binders (*group D*), air embolism did not occur in either of the two animals in a total of eight ascents. Although the intratracheal pressure was high under these circumstances, the intrapleural and left atrial pressures were also maintained at a very high level. The effect of the thoraco-abdominal binders is thus to keep the transpulmonic and transatrial pressure gradients low. That cardiac output fell far less than in *group C* is indicated by the relatively slight drop in systemic aortic pressure.

Threshold Pressures for Air Embolism. When all the animals that developed air embolism (*groups A* and *C*) are compared with those that did not (*groups B* and *D*), the critical levels of transpulmonic or transatrial pressure gradients emerge. When the transpulmonic gradient is less than 60 mm Hg, or the transatrial less than 50 mm Hg, air embolism does not occur, even if the intratracheal pressure reaches levels in excess of 90 mm Hg.

Relation of Pressure Gradients to Intravascular Pressures. The relation of transpulmonic and transatrial gradients to intravascular pressure is of interest, since it has been suggested that alterations in the latter may contribute to injury or death during decompression from depth. Such relationships are indicated in figures 5, 6, and 8. The animals in *groups A* and *B* are indicated by open circles, *group C* by triangles, and *group D* by black circles. The transpulmonic rather than the transatrial pressure will be the gradient of reference, since these have been shown to be closely parallel under the various conditions of

the experiments and the former datum is more easily obtained.

The general manner in which the transpulmonic pressure and systemic arterial pressure are related is shown in figure 5. With increasing transpulmonic pressure, the arterial pressure falls. The animals of *group C* have a somewhat higher relative pressure at the point of measurement in the abdominal aorta, perhaps for the reason that the pressure in this vessel is maintained by the high intra-abdominal pressure. Tables 1 and 2 show these relationships in a more general way. Obviously, it is not the absolute level of the intrathoracic pressure that produces the fall in systemic pressure, since the intrapleural pressure is very high in *group D* (thoraco-abdominal binders), the group in which the left atrial pressure also is highest, but the fall in systemic arterial pressure is hardly perceptible (see also fig. 4). In figure 6 is shown a similar relationship to venous pressure, but the scatter is more wide. The higher the transpulmonic pressure, the lower the systemic venous pressure. Again, the venous pressure appears to be relatively high for the transpulmonic pressure in *group C*. It may be surprising that the venous pressure should be low with a high transpulmonic pressure, but this follows from the fact that intrapleural and systemic venous pressures are more or less directly related (fig. 7). Since, by definition, the transpulmonic gradient is equal to intratracheal minus intrapleural pressure, the lower the intrapleural (or peripheral venous) pressure, the steeper will be the transpulmonic gradient for any given level of intratracheal pressure.

The effective pulmonary arterial pressure (defined as the pulmonary artery pressure minus the intrapleural pressure) becomes

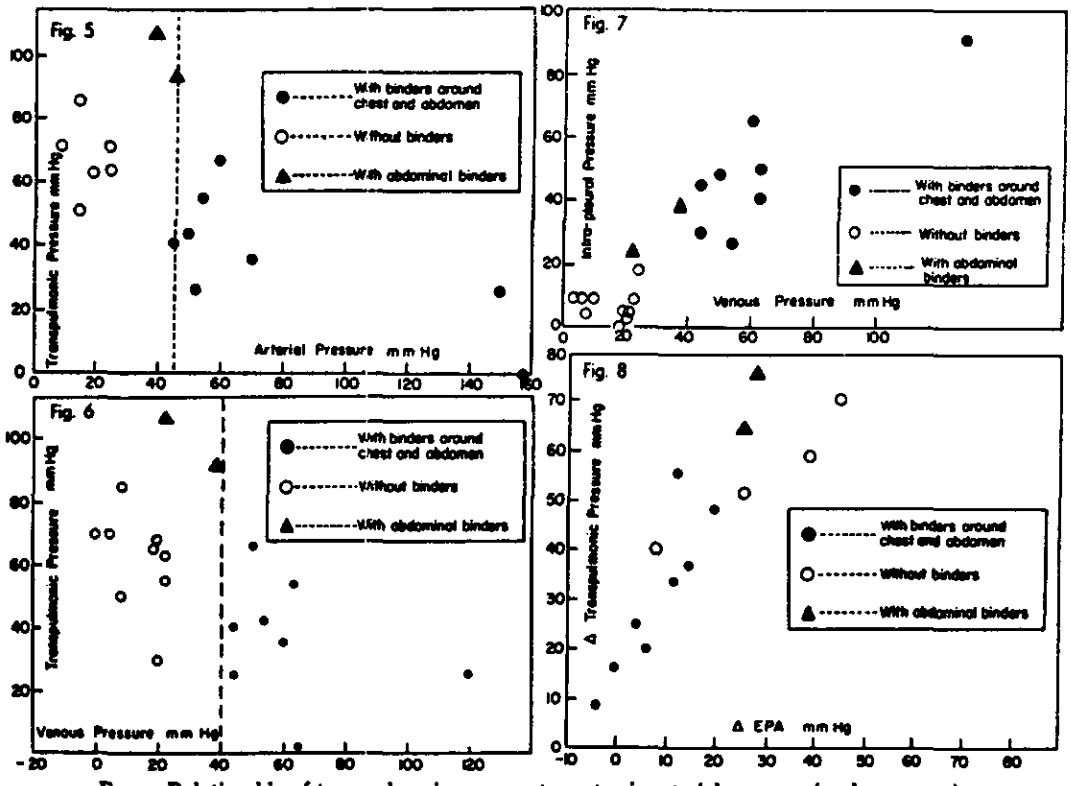

FIG. 5. Relationship of transpulmonic pressure to systemic arterial pressure (peak pressures).
FIG. 6. Relationship of transpulmonic pressure to pressure in inferior vena cava (peak pressures).
FIG. 7. Relationship of intrapleural pressure to pressure in inferior vena cava (peak pressures).
FIG. 8. Relationship of increase in transpulmonic pressure to increase in effective pulmonary arterial pressure (peak pressures).

elevated in step with the transpulmonic gradient (fig. 8).

It is obvious that, since the intra-atrial and intrapleural pressures tend to rise or fall in parallel, the difference between the two, in relation to any phenomenon that affects either of these, will show no significant displacement.

PART II

Evaluation of Protective Binders About Chest and Abdomen. Having defined the relationships between intracavitary and intravascular pressures during decompression from depth, another experiment was designed to test on a larger number of animals the value of binders about the chest and abdomen in simulated ascent from 200-foot depths with trachea closed and to attempt to establish the depth at which air embolism takes place. Each experiment was carried out with a pair of dogs, one with thoraco-abdominal binder and one without a binder. Data from six test and six control dogs relating intratracheal pressure to time and to depth in feet are charted in figure 9. The vertical line centered on each point provides the standard deviations of the intratracheal pressure readings and the central figures indicate the statistical *P* value of the difference of the means. With the use of the effective scissors clamp, the intratracheal pressure in the test animal rose to levels approaching 200 mm Hg. Despite this, the test animals wearing binders around chest and abdomen all survived the ascent. In the controls, the rise in the intratracheal pressure was parallel to that of the test group until a depth of approximately 20 feet was reached, whereupon there was a decline indicating escape of gases from the lungs with interstitial emphysema and air embolism. All of the control animals were found dead when the chamber was entered after the decompression, or they died shortly thereafter.

PART III

Observations at Necropsy. The pathologic findings are summarized in table 3. The four dogs listed in the lower section of the table as 'nonfatal instances' were killed with an overdose of Nembutal.

All the animals that died after decompression and also one of the nonfatal instances had interstitial emphysema; this invariably involved the lungs and, in most cases, the mediastinum and body wall, as well. 'Interstitial emphysema' is used here to indicate grossly visible trapping of gas bubbles in the loose connective tissue. Little can be added to the pathology or pathogenesis of this condition as described by the Macklins (16) in human and experimental material with 'over-pressure' in the respiratory passages. In the lungs, the bubbles varied from less than 1 mm to over 1 cm in diameter. Externally, they were most prominent in the interlobar fissures near the hilum and especially about the proximal portions of the pulmonary veins (fig. 10 and 11). These vessels were either collapsed or were seen to contain dark blood mixed with bubbles of gas. For the most part, the lungs collapsed at least partially and there did not appear to be so rigid a 'splinting' as to interfere with the

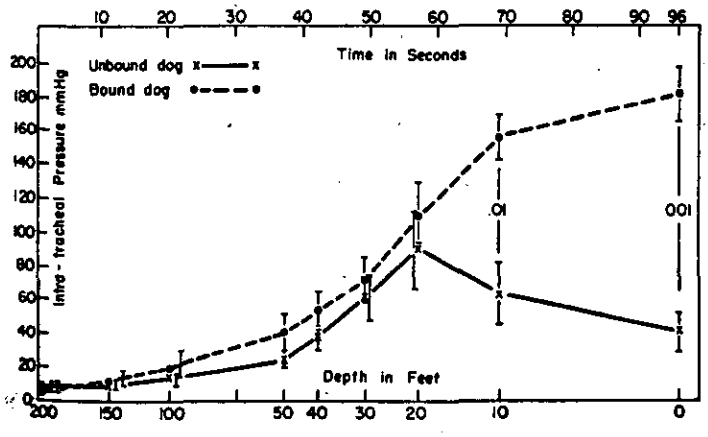

FIG. 9. Intratracheal pressures in dogs with thoraco-abdominal binders (solid line) and unprotected dogs (interrupted line) during decompression from 200-ft. equivalent depth. Each point straddled by vertical line that indicates range of observed values against ordinate. Statistical *P* values are indicated with reference to last 2 points.

TABLE 3. PATHOLOGIC FINDINGS IN DOGS AFTER DECOMPRESSION WITH CLOSED AIRWAY

Exp. No.	Necropsy	Gas in Bubble Traps		Heart Chambers		Gas in Vessels				Gas in Cavities			Interstitial Emphysema		
						Coronary		Cerebral	Subcut.						
		Carotid	Jugular	R	L	Aa	Vv			Pl / R-L	Pt	Pc	Lung	Med.	Body wall
						Fatal Instances									
3	C	+	+	+	+	+	+	+	+	+ +			+	+	+
4	X	+	o	+	o	+	+		+				+	+	+
9	CB	+	+	+	+	+	+	+	+	+ +	+	+	+	+	
10	C	+	o	+	+	+	+		+	+ +	+	++	+		
14	C	+	+	+	+	+	+			+ +			+	+	+
15	X	+	o	+	+	+	+			+ +	o		+	+	
20	X	o	o	o	o	+	o			o +			+	+	
22	X	+	o	+	+	+	+		+	+ +				+	o
23		+	+	+	+	+	+						+	+	+
26	C	+	o	+	+	+	+			o o	o		+	o	+
						Non-Fatal Instances									
5	CB	o	o	o	o	o	o	o		+ +			+	+	+
8	CB	o	o	o	o	o	o	o		+ +			o	o	o
11	X	o	o	o	o	o			o	o o	o	o	o	o	o
12	X	o	o	o	o	o	o					+			
13	X	o	o	o	o	o	o			o o			o	o	o

Experiments 3–13 inclusive, decompression from 100 ft. equivalent depth; others 200 ft.

C = chest opened under water; CB = chest and cranium opened under water; X = ordinary necropsy; Pl = pleura; Pt = peritoneum; Pc = pericardial sac.; *o = definitely not* present; blank space = observation not recorded; Aa = arteries; Vv = veins.

respiratory movements. It must be recalled, however, that splinting may well have existed while the pressure in the trachea was still elevated and before decompression had occurred into the blood stream with the development of air embolism and into the pleural cavities with the occurrence of pneumothorax. Clearcut evidence of 'air block', however, was the presence on all cut surfaces of innumerable gas bubbles in the pulmonary septa and about the broncho-arterial rays, with collapse of both arteries and veins (fig. 12). The thin walls of the bubbles as they surrounded the vessels had the appearance of a spider's web. Extravasated blood was present in the areolar connective tissue. It was not present in every case, nor everywhere within a lung. The hemorrhage evidently was the result of trauma by gaseous dissection in a heparinized animal and was distributed as a sleeve about the vessels. It was interstitial, rather than within the respiratory passages and was, moreover, as prominent on the right side as on the left. It was much more apparent on the cut surface of the lung than on the pleural aspect. Interstitial emphysema ordinarily is accompanied by little, if any, hemorrhage. In a few instances, the visceral pleura was elevated by scattered hemispherical blebs with a greatest diameter not exceeding 1 cm. These were covered by a diaphanous membrane and resembled soap bubbles. In no instance was it possible to identify a single site of origin for the dissecting gas which probably arose at multiple or innumerable points (16). Once dissection began, however, the connective tissue planes in the pleura, septa and broncho-arterial rays, in particular, seemed to be easily followed to the hilum and mediastinum. There was obvious continuity across the mediastinum from one lung to the other.

An accurate estimation of the presence or significance of pulmonary edema is difficult in any event, and especially under circumstances of long continued anesthesia and repeated compression and decompression. Pulmonary edema was, however, in no instance massive, although focal congestion and slight extravasation of fluid sometimes accompanied the interstitial emphysema (fig. 11).

Pneumothorax usually accompanied the pulmonary interstitial emphysema and when it occurred, it was bilateral except in a single

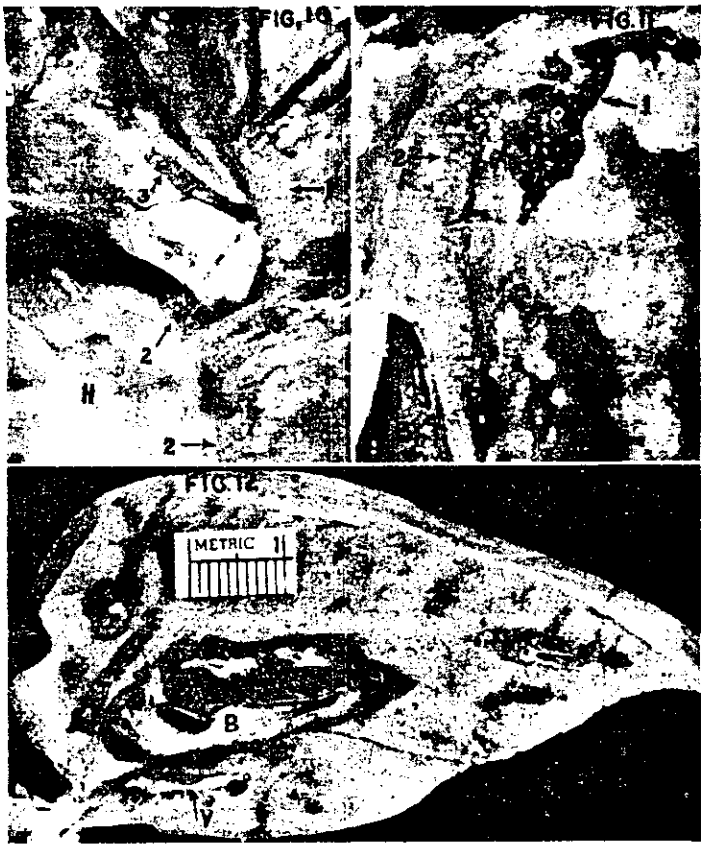

FIG. 10. Left lung, anterior and mediastinal aspect; heart. Interstitial emphysema and air embolism. *1*, Gas bubbles in hilar subpleural connective tissue. *2*, Gas bubbles at reflection upon pericardial sac. *3*, Gas bubbles in lumen of pulmonary vein. *H*, Heart covered by pericardial sac.

FIG. 11. Left lower lobe, anterior and mediastinal aspect. Interstitial emphysema. Large gas bubbles at hilum of lung *1* and in contiguous mediastinal tissues *2*. Focal pulmonary congestion is evident. Tissues had bogginess suggestive of pulmonary edema. *E* = esophagus, outer coats of which also contain bubbles of gas.

FIG. 12. Interstitial emphysema. Vessels are collapsed by bubbles of air that dissect perivascular areolar tissue. Smaller bubbles are found in outer coats of bronchi. There is hemorrhage, probably increased by heparinization of animal, in connective tissue that has been dissected by gas. *A* = pulmonary artery; *V* = pulmonary vein; *B* = bronchus.

instance (table 3). This bilaterality suggests the origin of the gas in the lung rather than from the catheterization of the pleura. There was, however, one animal in the nonfatal series in which pneumothorax was bilateral in the absence of interstitial emphysema in lung or mediastinum. A minor degree of this condition may, however, have been missed on gross inspection.

The mediastinum contained dissecting gas in all cases where there was pneumothorax, and in every instance but one where the interstitial tissue of the lung contained gas. This observation is compatible with the view expressed by the Macklins (16) that pneumothorax arises as a rule by the dissection of air from the mediastinum, rather than directly from the lung. Dissection by gas of the mediastinal connective tissue also accounts for occasional penetration into the pericardial sac and peritoneum (fig. 10).

Except for the presence of gas in the vessels, when this was demonstrated by appropriate methods, there were no significant lesions in the brain, nor would one expect to see any but the coarsest changes in the brief interval between the trauma of decompression and death. Fat emboli were sought in frozen sections stained with Sudan IV, but none were found. This and other mechanisms of injury in rapid decompression are discussed in Haymaker's excellent review (17).

That the air embolism occurred by way of the pulmonary veins, left heart and systemic arteries is suggested by the fact that the carotid bubble traps contained gas bubbles while the jugular might not, but the opposite was never encountered (table 3). The mechanism of death was not from 'pulmonary block', as appears to be the case when air is introduced in quantity into the systemic veins (18).

DISCUSSION

The present work is an extension of the observations of Pollak and Adams (12). Their conclusions are confirmed that the critical intratracheal pressure for the development of air embolism in unprotected animals is approxi-

mately 80 mm Hg and that the protective effect of binding the thorax depends upon the prevention of distention of the lung. In the current experiments, the distention was quantitated on the basis of the transpulmonic pressure gradient, defined as the difference between the intratracheal and intrapleural pressure. A high intratracheal pressure, for example, 180 mm Hg or more, can safely be withstood, as long as the transpulmonic pressure does not exceed a critical level of approximately 60 mm Hg. It is reasonable to conceive that the actual significant gradient is that between the intrapulmonic pressure and the pressure in the pulmonary veins—the 'transatrial pressure'. This gradient has been demonstrated to run parallel to the transpulmonic gradient in the course of the experiments reported here. The latter is more easily determined than the transatrial and is, therefore, more conveniently used as a standard of reference.

In the present experiments, both lungs have been subjected to the stresses imposed by expanding and trapped intra-alveolar gases, with resulting interstitial emphysema and air embolism under certain circumstances. It is perfectly possible, however, that similar untoward effects can occur from air entrapped within a relatively small part of the lung. In man, partial valving mechanisms are responsible for some types of emphysema. In fact, any condition in which bronchi are narrowed tends to trap air. This can occur chronically or it can be induced acutely by the production of exudates or excessive quantities of viscid mucus. Any bronchus which is at all expansible will have a larger lumen during inspiration than during expiration. Resistance to flow of air is, therefore, greater during the expiratory phase by a factor inversely proportional to the fourth power of the radius. It is also possible that bronchospasm, local or generalized, may have similar functional effects. The problem of trapped air in the lungs, which has received considerable attention in recent studies of DuBois *et al.* (19, 20), appears to be of practical importance for the development of air embolism under the conditions of escape training. In one recent instance of fatal air embolism which occurred at the Escape Training Tank, a calcified broncholith acting as a valving mechanism could be demonstrated. In another recent patient, in whom symptoms of air embolism were successfully treated with recompression, evidence of existing local lung pathology was provided radiographically. When air is trapped, even in some small pulmonary segment wherein the critical transpulmonic pressure is reached, air embolism could arise even under the conditions of a 'normal' ascent, without breath holding or generalized obstruction of the airways. It appears unlikely that a compressive binder such as a 'G-suit' would have a protective effect against air embolism consequent to local air trapping, but this remains to be determined by experiment.

An additional, untoward effect of decompression from depth with airway closed in unprotected animals is a fall in systemic arterial pressure. That this is dependent in part on a rise in vascular resistance in the lung is suggested by the increased gradient between the pressures in the pulmonary artery and left atrium (transcapillary pressure) in those animals that developed air embolism, *groups A* and *C* (table 2). This statement is based on the assumption that blood flow is no greater in animals of *groups A* and *C* than in those of *groups B* and *D*. Such a period of systemic hypotension obviously becomes increasingly harmful the longer it persists. Over intervals of 2 minutes or less it will not be fatal nor will it produce permanent harm. If hypotension of the observed degree were to develop in a previously conscious subject it is likely, however, to result in a 'blackout'. After release of the tracheal obstruction, the systemic arterial pressure is promptly restored in animals that are destined to recover. Whatever the untoward consequences of hypotension, one of the beneficial effects of the thoraco-abdominal binders is the maintenance of the aortic pressure with little fall throughout the 'ascents'.

For a time during the course of these experiments it was thought that air embolism first became manifest by a sudden drop in pulmonary arterial and venous pressure. This sign, however, was found also in dogs which did not develop air embolism. Others (personal communication from Dr. R. E. Elias) have demonstrated in experiments in which the lungs were overdistended that, after a transient rise in pulmonary artery and venous pressure, a fall in these pressures occurs, associated with a reduction in cardiac output and coronary blood

flow. Thus, a fall in the intratracheal pressure is the only true indication that air embolism has occurred. Previous pressure drops in the pulmonary arteries and veins become reversed at the moment when the intratracheal pressure begins to decline. It is when blood flow starts again that the bubbles are presumably transported into the coronary or cerebral vessels with ultimate fatality. In animals that develop air embolism, the systemic arterial pressure does not recover significantly, but undergoes a permanent fall after a preliminary rise upon opening of the airway. The appearance of the first air bubbles in the carotid bubble trap could not be timed accurately since the compression chamber becomes filled with mist as the pressure is released.

In some instances, the systemic venous pressure, upon opening the tracheal valve, reached remarkably high levels, in the range of 50/10 mm Hg, and the pressure waves closely resembled those of the aorta. This suggests a relative tricuspid insufficiency, probably occasioned by a greatly increased venous return and abetted perhaps by a preceding phase of myocardial anoxia. This phenomenon was inconstant. In other instances, the pulmonary artery or aortic pressure underwent an 'overshoot', perhaps also the result of an increased cardiac output.

Since the exposure time at 100 or 200 feet was only 1 minute, conditions for occurrence of decompression sickness, with an appreciable solution of gases in blood and tissue, were avoided even in those animals that were subjected to as many as seven compressions at 100 or 200 feet.

To be investigated is the existence of reflex effects of altered pressures in various segments of the circulation (11) and possible effects of altered gas tensions as they exist over short intervals of time.

Simple inflation of the lungs, as done, for example, by Bjurstedt and coworkers (7–9), differs from the conditions during compression and 'ascent', as simulated by the present procedure, in that the body as a whole is affected in the latter. The Bjurstedt group observed a large pressure gradient between thorax and abdomen and a fall in pulmonary arterial and systemic arterial pressure and concluded that the blood was 'pooled' in the abdomen. In the present experiments, however, when the high pressure and subsequent decompression are made to affect the entire body, there is at first a closer approach of intra-abdominal and intrathoracic pressures and the pulmonary arterial pressure at first rises in all instances upon decompression. Here the development of pressure inside the body is produced by the reduction in pressure outside and the body as a whole, including intestinal gases, is affected.

The authors express their appreciation to Drs. Robert C. Stroud and Richard Elias for critically reading the manuscript.

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ARCHIVES OF SURGERY

VOLUME 19 OCTOBER, 1929 NUMBER 4

AIR EMBOLISM FROM THE PULMONARY VEIN

A CLINICAL AND EXPERIMENTAL STUDY *

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Air embolism, with the pulmonary vein as the portal of entry, may complicate nearly any surgical procedure on the lung. Graham [1] experienced two fatalities from this source in forty-five operations of cautery pneumectomy, and it has occurred in as simple a procedure as irrigation of an empyema cavity. Brauer [2] termed the condition arterial air embolism and emphasized its frequence as a complication of artificial pneumothorax. While the cause of the syncope, collapse and death that are occasionally seen during pneumothorax induction is not always clear, it is doubtless often air embolism. Stivelman [3] reported seven instances occurring in 162 primary punctures; Forlanini [4] had twelve in 134, and Sachs [5] collected twenty-two in 1,122 from the literature.

Sharp distinction must be made at once between this form of air embolism and that in which air enters a peripheral vein, as the jugular or subclavian. In the former, air enters the peripheral arteries and may involve every organ and tissue, while in the latter air passes into the pulmonary arteries and exerts its effects on the lesser circulation and right side of the heart.

In this article are presented certain clinical and experimental data and deductions concerning air embolism from the pulmonary vein. A brief summary of current knowledge is given to introduce each phase

* Submitted for publication, May 13, 1929.

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of the subject. Complete reviews of the literature are available elsewhere.[6]

ETIOLOGY

Air may enter the pulmonary vein spontaneously or may be injected.

The venous pressure in the pulmonary circulation is ordinarily less than that of the atmosphere, and should the lumen of a vein be freely opened air is drawn into the blood stream. This has occurred in such operations as pneumectomy, pneumotomy, pulmonary decortication, dissection or probing within the lung and separation of the pleural adhesions. Injection of air or other gases directly or indirectly into the circulation has occurred in the production of artificial pneumothorax. The needle may accidentally enter the lung and one of its vessels, or when the puncture has been accurate and the gas enters the pleural cavity an adhesion between the lung and the wall of the chest may tear and open a pulmonary vein. Air from the pleural cavity may then enter the torn vessel.

Essentially the same type of embolism has been known to arise in other ways: Air that has entered a peripheral vein and has been carried to the right side of the heart occasionally finds its way through a patent foramen ovale into the left auricle.[7] That the foramen ovale is frequently patent without evidence during life is well known. Herxheimer [8] found from 20 to 50 per cent patent during routine examination at autopsy; Otto [9] noted 286 in 1,130 consecutive autopsies in Dresden material, of which 200 admitted a probe only and eighty-six were of comparatively large size; Lubarsch [10] found patency in 25 per cent, and Kaufmann [11] in 32.5 per cent.

In 1808, Bichat [12] demonstrated that when air is blown into the lungs of a living animal at a pressure no greater than the maximum expiratory effort of which the animal is capable, provided the pressure is maintained, air will leave the alveoli and enter the pulmonary capillaries. Enough air may thus be forced into the circulation to cause death, and the effect is, of course, the same as though the air had directly entered a pulmonary vein. Ewald and Kobert,[13] in a painstaking study,

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"Ist die Lunge luftdicht?," showed that this phenomenon is not one of alveolar rupture but of escape of air through normal stomas in the alveolar walls when a certain degree of distention is reached. On this principle has been explained the finding of air occasionally in the cavity of the left side of the heart of persons drowned [14] or hanged [15] and of infants who have received strenuous resuscitative measures.[16] Neubürger [17] suggested that the convulsions which sometimes occur in whooping cough are from cerebral embolism, air being forced into the blood stream from the alveoli during a paroxysm of coughing. At autopsy in these cases confirmatory evidence is found in the lesions of the brain.[18]

CLINICAL CASES

CASE 1.—A man, aged 42, had an illness of sixteen months' duration. The onset was insidious, with cough, fever, night sweats and progressive loss of weight. The sputum was abundant and fetid, and was constantly negative for tubercle bacilli. The diagnosis was bronchiectasis of the left lung and chronic empyema.

He was admitted to University of Iowa Hospital surgical service. A small empyema pocket in the left side of the chest was drained by rib resection. Some time later, by roentgen examination, a cavity was found in the left lung, and surgical drainage of the cavity was undertaken. With the patient under ethylene anesthesia, a piece of rib was removed at the posterior axillary line over the cavity. The pleural surfaces were found adherent, and an exploring needle, attached to a syringe, was passed into the lung. The resistance offered to the needle by the parenchyma of the lung was increased. At some points air was aspirated freely, at others blood. No pus was found and after a few punctures the attempt was abandoned. As the wound was being closed, the patient suddenly ceased to breathe and heart action could not be detected.

At autopsy, about one hour after death, air was found in large quantities in the blood vascular system. The right side of the heart and pulmonary artery were distended with bloody froth. The left side of the heart was empty. Air was present in the aorta and its main branches, and beads of air were plainly visible in the coronary arteries, the mesenteric arterioles and such small arteries as were exposed by dissection. The veins everywhere were free from air, except for the portal vein and the great veins near the right side of the heart, which contained large amounts. The left lung was fibrous, contracted and adherent to the wall of the chest throughout, except where there was a small empyema cavity. This cavity communicated with the surface through an old thoracotomy wound. After the left lung was removed, the integrity of its bronchial tree was tested by filling it with water. The water returned immediately by way of the pulmonary vein of the upper lobe. In the left primary bronchus was found a papillary carcinoma nearly obstructing the lumen. On section, the lung proved to be fibrotic throughout and was riddled with saccular bronchiectatic cavities. Dissection failed to show a precise point of communication between the bronchial tree and the pul-

14. Paltauf, quoted from Walcher, K.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **29**:314, 1926.

15. Iversen, A.: Vrtljschr. f. gerichtl. Med. **22**:226, 1862.

16. Lindblom, A.: Virchows Arch. f. path. Anat. **252**:197, 1924.

17. Neubürger, K.: Klin. Wchnschr. **4**:113, 1925.

18. Husler, J., and Spatz, H.: Ztschr. f. Kinderh. **38**:428, 1924.

monary vein, although a clot of fresh blood was found in a bronchiectatic cavity in the upper lobe at a point roughly corresponding to the site of thoracentesis. The right lung was normal, and observations elsewhere were unimportant.

The diagnosis was: carcinoma of the left primary bronchus, bronchiectasis, chronic empyema, bronchovenous fistula and air embolism from the pulmonary vein.

EXPERIMENTAL WORK

Proof by experiment was sought for the theorem suggested by this case: Given a bronchovenous communication, the pressure relationships within the bronchi and veins in a closed chest during life are such as to transfer air from bronchus to vein. Four dogs were used. A bronchovenous fistula was produced within the intact chest in such a manner that communication could be established or abolished at will and the passage of substances through the fistula could be observed.

Dog 1, weighing 10 Kg., was given positive pressure ether anesthesia. The chest was opened through an intercostal incision on the right and the hilum of the lung was exposed. A glass cannula filled with sodium citrate solution was tied into the pulmonary vein of the lower lobe. Another cannula was fixed in the wall of the accompanying bronchus, and the two cannulas were led out of the chest and connected with a short piece of rubber tubing, temporarily clamped off. The lungs were then inflated to exclude pneumothorax and the chest wound closed tightly about the cannulas. The dog was then allowed to recover consciousness fully.

While the animal was walking about, the clamp was suddenly removed from the connecting tube and communication was established between the bronchus and vein. With the next inspiration, the solution in the cannula passed quickly into the vein and was followed by air, as evidenced by the behavior of a little solution that remained in the bend of the tube. The next two or three inspirations each drew more air into the vein, and then the flow was reversed filling the tube with blood. Almost immediately after the first inspiration the dog appeared uncomfortable, and the hind quarters began to drag; paralysis spread and in a few seconds the dog fell to the floor unconscious. There followed focal and general convulsions, labored breathing, extreme rotation of the eyeballs and wide dilatation of the pupils. At about three minutes, muscular relaxation occurred, respirations became feeble and soon ceased. Heart action continued for a minute or so.

Autopsy revealed that the relations within the chest were normal except for the artificial connection between the bronchus and vein. Quantities of air were contained in the vascular system.

DEDUCTIONS

A bronchovenous fistula may be created in man by the passage of an exploring needle into firmly indurated lung tissue. Given such a communication, the relation of bronchial to venous pressures during inspiration is such as to pass air from bronchus to vein and to give rise to fatal air embolism.

DISTRIBUTION OF AIR IN THE CIRCULATION

Gundermann [19] opened the chest of dogs widely with the animals under positive pressure anesthesia and injected air directly into a

19. Gundermann, W.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. 33:261, 1921.

pulmonary vein. It appeared to him that the air was distributed by the heart evenly and in proportion to the size among the peripheral arteries, until just before death, when because of a weak heart action the branches of the aorta lying near the heart received a larger share. He observed air bubbles immediately entering the coronary arteries and riding there without a tendency to pass on through the capillaries, and he concluded that air cannot pass any capillary bed. Heller, Mager and von Schrötter,[20] on the other hand, observed air bubbles travel through the mesenteric circulation, and Beneke [21] found air accumulated in large quantities in the right side of the heart, when injection had been made into the peripheral arteries.

That position of the body affects in some degree the distribution of the air in this form of air embolism was suspected by Schlaepfer,[22] for he noticed that bubbles could be seen in the retinal vessels of dogs only when the head was held up.

EXPERIMENTAL WORK

The distribution of air received into the pulmonary veins in the vascular tree was studied in dogs under varied circumstances of dosage and body position. The manner of inducing embolism was uniform: With the animals under positive pressure anesthesia, the chest was opened and a glass cannula, filled with sodium citrate solution and temporarily obstructed at the outer end, was fastened in the branch of the pulmonary vein from the lower lobe of the lung and led out of the chest. The chest was closed, residual pneumothorax being avoided. The anesthetic was then discontinued and air was injected through the cannula with a syringe at a uniform rate of 25 cc. per minute. At death, or when the animal was killed, a systematic examination was made of the vascular system.

The experiments may be grouped in accordance with the position of the animal. Representative protocols are as follows:

Group 1: Position Horizontal, Sixty-Seven Dogs.—EXPERIMENT 1.—Dog 21, weighing 16 Kg., was placed on the left side in the horizontal position, and an amount of air equal to 3.9 cc. per kilogram of body weight was injected into the pulmonary vein. Death occurred in nine minutes.

At autopsy, the right side of the heart and adjacent great veins were found moderately distended with air. The pulmonary arteries were filled with air; the left side of the heart and pulmonary veins were free. There were a few air bubbles in the coronary arteries and veins. The aortic arch was partly filled with air, but the descending aorta throughout contained none. The carotid, axillary, internal mammary, intercostal and femoral arteries on the right side

20. Heller, R.: Mager, W., and von Schrötter, H.: Ztschr. f. klin. Med. **32**: (suppl.) 113, 1897.

21. Beneke, R.: Verhandl. d. deutsch. path. Gesellsch. **16**:263, 1913.

22. Schleapfer (footnote 6, first reference).

considerable amounts of air, while the corresponding vessels on the left were relatively free. The mesenteric arteries were beaded with bubbles. Air was found only in the femoral, portal, internal mammary and jugular veins.

In other dogs of this survival time the distribution of air was essentially the same. Those dying more rapidly (in from one to two minutes) showed air still in the left side of the heart and confined largely to the arteries. Little was found in the large veins or right side of the heart. Animals living longer than dog 21 (from twenty to thirty minutes) had little or no air in the right side of the heart and veins and reduced amounts in the peripheral arteries. The coronary arteries were regularly free. A constant and striking observation was unequal distribution, for vessels lying uppermost in the body, here in the right side, were always much more abundantly supplied with air. This evidence of air buoyancy

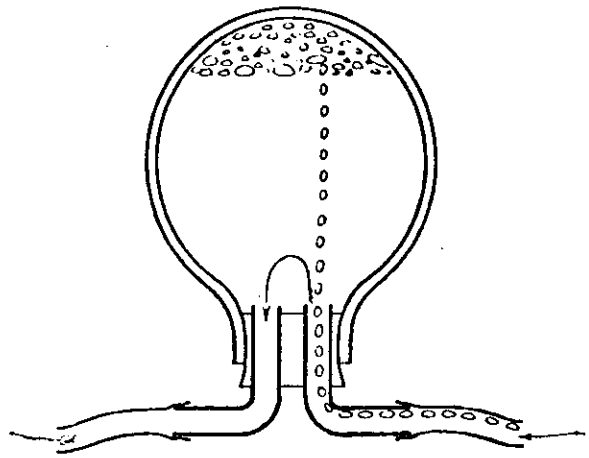

Fig. 1.—Air trap used to study the distribution of air.

was displayed also in the aortic arch. The first portion of the arch lay uppermost and accumulated air from the blood passing through. This air drained off largely into the great vessels of the neck, and the result was to distribute a greater portion of the air to the head, neck and upper extremities than would be indicated from the size of the vessels.

In a few of these dogs, the distribution of air was studied more exactly by interposition of air traps in the blood stream at various points. The air trap (fig. 1) was a small inverted flask with afferent and efferent cannulas. The circulating blood was rendered incoagulable by the intravenus injection of 20 mg. of heparin per kilogram of body weight. The vessel in question was then exposed and divided and the two ends connected with the trap cannulas, the trap being first filled with blood. When adjusted, the trap thus became a part of the vascular system, and by retaining air which passed through the vessel permitted estimation of its appearance time and amount.

EXPERIMENT 2.—Dog 65, weighing 13 Kg., was fitted with traps in both carotid arteries. Three and nine-tenths cubic centimeters of air per kilogram of body weight (50.7 cc.), which is a lethal dose, was injected into the pulmonary vein in the routine manner. Almost instantly after the injection was started air bubbles began to appear in the traps and continued to do so only as long as the injection lasted. The dog recovered; it was killed at one hour.

At autopsy, air was found distributed in the vessels as usual, except that the carotid arteries were free. Twenty-seven cubic centimeters of air was recovered from the traps, i. e., more than half that injected.

EXPERIMENT 3.—Dog 38, weighing 12 Kg., was fitted with traps in both vena cavae, and 3.9 cc. of air per kilogram of body weight (46.8 cc.) was injected into the pulmonary vein. At one minute and twenty seconds, bubbles of air began to appear in the trap of the superior vena cava. No air entered the other trap. Death occurred in ten minutes.

Autopsy showed air to be distributed in the usual manner, except that the right side of the heart and pulmonary arteries were free. Three cubic centimeters of air was present in the trap of the superior vena cava. This amount could obviously not be taken to represent the quantity ordinarily returning to the heart after this dosage of air, since the presence of the traps in the cavae impeded the driving force of the heart to a considerable degree.

Group 2: Position Vertical, Head Down, Sixty-Six Dogs.—Dog 109, weighing 17 Kg., was raised to a vertical position, head down, and 3.9 cc. of air per kilogram of body weight was injected into the pulmonary vein. Death occurred at seventeen minutes.

Autopsy revealed that air filled the coronary arteries and the arteries and veins of the trunk and hind legs. None was found in the vessels of the head, neck and forelegs, nor in the vena cavae, right side of the heart or pulmonary arteries.

In all of these animals, the pattern of distribution was constant. The vessels caudad to the heart alone received air. The coronary arteries contained much more air than with the dog in the horizontal position, and often the blood was entirely replaced by air, giving the vessels the appearance of silver threads. Occasionally, the left ventricle, being inverted, retained a considerable quantity of air indefinitely. No air returned to the right side of the heart.

The observations were corroborated in part by experiments using traps in various vessels.

Group 3: Position Vertical, Head Up, Nineteen Dogs.—Dog 47, weighing 5.5 Kg., was placed in a vertical position, head up, and 3.9 cc. of air per kilogram of body weight was injected into the pulmonary vein. Death occurred in five minutes.

Autopsy revealed that air filled the vessels of the head, neck and forelegs. A small amount was found in the right side of the heart and pulmonary arteries and a few bubbles of air only were contained in the coronary arteries.

In this group of animals again a constant pattern of air distribution was presented, which was complementary in type to that for the group with the head down. Only the vessels taking origin from the aorta cephalad to the heart received air. The coronary arteries were involved to a minimal degree.

DEDUCTIONS

Air that enters the circulation by way of the pulmonary vein follows the course of the blood stream in general but with uneven distribution. Instead of being divided among the vessels in amounts according to their sizes, the air tends to float on the blood and to seek the upper parts of the body. Even where the stream is rapid and violently churned, as in the heart and aorta, air and blood fail to mix thoroughly; the air may remain stationary in a bend of the vessel, or, should gravity so dictate, it may even pass in the direction opposite to that of the blood.

This influence of air buoyancy on the distribution determines distinct differences in various positions of the animal. A typical pattern of embolism with but slight individual variation is found in any given position. Thus, in the dorsal recumbent, horizontal position, air quickly leaves the pulmonary vein and left side of the heart and passes into the aorta. The arch of the aorta is distinctly higher than the descending portion of that vessel and acts as a trap to hold a large part of the air and pass it into the great arch branches. Thus, more than half of the air may go to the head, neck and upper extremities. Distributed in this uneven manner, the air in the form of bubbles is driven to the periphery. The capillaries hinder but do not prevent passage, and after a minute or so air begins to return by the veins of the parts affected to the right side of the heart, whence it is thrown into the lesser circulation. No air succeeds in traversing the pulmonary capillaries but it is held in the pulmonary arterial tree, obstructing the lesser circulation partially and gradually disappearing by excretion into the alveoli and by absorption into the blood and tissues. Air remains longest in the peripheral arteries, sometimes for several hours, for a shorter period in the pulmonary arteries, right side of the heart and great veins, no longer than one-half hour in the coronary arteries and for only a few seconds in the pulmonary veins and left side of the heart. Thus, the period of time that elapses between embolism and death determines largely the position of the air at autopsy.

With the animal in a vertical position, air is distributed only to those parts lying above the level of the heart. Accordingly, when the head is up, the head, neck and forelegs receive the air totally, except for a slight amount in the coronaries; when the head is down, the trunk and hind legs receive the air, and the coronaries are heavily involved.

PHYSIOLOGIC REACTION, TOLERANCE AND CAUSE OF DEATH

The symptoms in man in air embolism from the pulmonary vein are separable more or less distinctly into two types, neuromuscular and cardiovascular. In a given case, both types may be equally represented, or one may predominate even to the exclusion of the other.

The nervous symptoms are extremely various and occur in different combinations in each instance. The onset may be precipitous with immediate unconsciousness and death, or it may be ushered in more gradually, beginning with dizziness, faintness, local or general paresthesias, aphasia and visual disturbances. More serious symptoms are paraplegia and hemiplegia, blindness, focal and general convulsions, unconsciousness, hyperpnea, Cheyne-Stokes respiration and unequal, dilated and reactionless pupils. Death may occur at any time, and has been known to be delayed as long as six days. When delayed, an unconscious state predominates with periodic convulsions. At any stage, the symptoms may begin gradually to disappear and the patient to recover. Persistent paralyses have occurred.

Cardiovascular symptoms consist in pulse irregularities, asphyxial signs and evidences of gradual or sudden heart failure. Patches of marble-like discoloration are sometimes found on the skin. These symptoms are seen alone when the patient is under general anesthesia and nervous reactions are inhibited, or when the amount of air is overwhelming and nervous effects do not have time to develop. Detailed discussion and illustration of symptoms are given by Schlaepfer.[22]

The degree of tolerance in man for air entering the circulation from the pulmonary vein is not known, although it is understood to be much less than that from a peripheral vein. In certain instances, as in the case reported by von Adelung,[23] the amount of gas injected for pneumothorax at the time of air embolism was known, but what part of that actually entered the circulation could not be determined. In animals, Gundermann [19] alone has estimated tolerance. Using dogs, he opened the chest with the animals under positive pressure anesthesia and injected air into a pulmonary vein, and found that even 1 cc. slowly introduced was immediately fatal. The unnatural circumstances of the experiments, however, probably rendered the animals abnormally susceptible.

It is generally appreciated that the tolerance of a person for air embolism depends largely on the rate of entrance of air into the circulation.

In air embolism from the peripheral vein the tolerance has been studied experimentally by several investigators. Ilyin [24] noted that dogs withstand as much as 2,000 cc. of air injected into the jugular vein at a rate of 30 cc. per minute with 10 mm. of mercury pressure. The dose per kilogram of body weight was not estimated. In twenty-five rabbits, Jehn and Nägeli [25] found the maximum tolerance to be 0.89 cc.

23. Von Adelung, E.: A Case of Gas Embolism, J. A. M. A. **69**:1522 (Nov. 3) 1917.

24. Ilyin, F.: J. Akush. i Jhensk. Bolïez. **28**:72, 1913.

25. Jehn, W., and Nägeli, T.: Ztschr. f. d. ges. exper. Med. **6**:64, 1918.

per kilogram of body weight; in six cats, 2.5 cc. per kilogram; and of two dogs, one survived 5.3 cc. and one died from 7.7 cc. per kilogram. The rate of the injection was not given. Richter [26] stated that in dogs 20 cc. of air produced alarming symptoms and 250 cc. was lethal; in horses, the corresponding amounts were 1,000 and 8,000 cc. No body weights, injection rates or numbers of animals were given. Many other investigators have contributed less accurate data. It is to be concluded that different species present widely different tolerances and among individuals of a single kind there is variation. The values in man are again not known.

The cause of death in air embolism from the pulmonary vein was referred by Gundermann [19] to heart failure, after observing in his dogs immediate myocardial incapacity following the entrance of air into the coronary arteries. He pointed out that heart action ceased too soon to allow involvement of the brain to play a part. Beneke,[27] at autopsy in man, found much air in the right side of the heart and pulmonary arteries and suggested that death was due to obstruction of the lesser circulation, as in air embolism arising from a peripheral vein. The fallacy of this assumption was indicated by Gundermann in the fact that an amount of air which is lethal when entering the pulmonary vein is readily tolerated when injected into a peripheral vein. The majority of authors agree with Brauer [28] and his school in ascribing death to brain embolism, since nervous symptoms frequently predominate and at death respirations usually cease long before heart action. Wever [29] injected air into the carotid artery of dogs and monkeys and produced a symptom complex similar to that of man. The brains of Wever's animals were examined by Spielmeyer.[30] Those that survived more than fifteen hours presented focal ischemic necrosis distributed irregularly, chiefly in the cerebral cortex, and characterized by degenerative alterations in the ganglion cells and glial proliferation. The degree was in proportion to the amount of air and to the period of time between embolism and death. The same changes were found in cases in man. Gold [31] described the brain of a person who died six days after cerebral air embolism, and in addition to the alterations mentioned, indicated edema of the whole brain and petechial hemorrhages in the medulla oblongata and pons.

26. Richter, quoted from Hutter, K.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **40**:131, 1927.

27. Beneke, R.: Beitr. z. Klin. d. Tuberk. **9**:343, 1908.

28. Brauer (footnote 2, second reference).

29. Wever (footnote 6, second reference).

30. Spielmeyer, W.: Verhandl. d. Kong. f. inn. Med. **30**:359, 1913.

31. Gold, E.: Arb. a. d. neurol. Inst. a. d. Wien. Univ., 1924, vol. 26.

CLINICAL CASES

Case 1, already described, illustrates the purely cardiovascular type of symptomatology, and case 2, to be described, the neuromuscular type.

EXPERIMENTAL WORK

Physiologic Reaction.—The reaction of the dog to air injected into the pulmonary vein was studied under varied experimental circumstances. The doses, determined according to the body weight, ranged from amounts easily borne to those immediately fatal. Three positions were employed, as in the preceding experiments. The method was the same in all instances:

A cannula was placed in a pulmonary vein. The femoral artery was cannulated and connected with a mercury manometer. With the

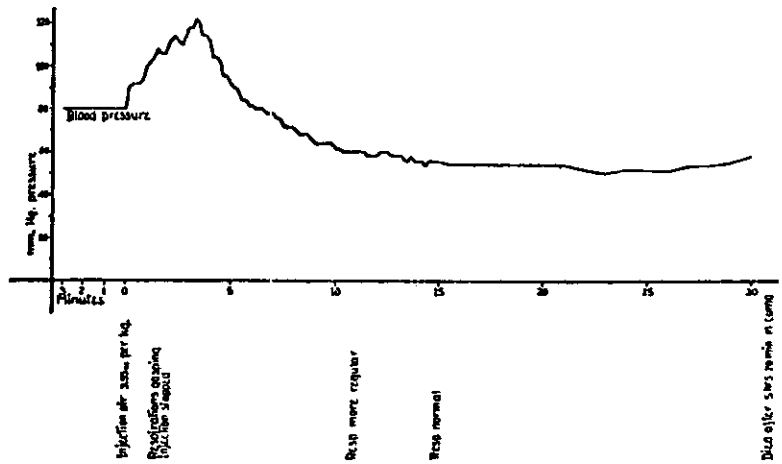

FIG. 2 (dog 20).—Injection of air into the pulmonary vein, with the dog in the horizontal position. Moderately severe reaction.

animal under ether anesthesia, respiration and blood pressure were observed, and when they had been constant for three minutes, the ether mask was removed and the dose of air injected into the cannula of the vein at a rate of .25 cc. per minute. The reaction was noted in detail.

Typical protocols are as follows:

Group *a*: Position Horizontal, Sixty Dogs: EXPERIMENT 1.—Dog 20, weighing 16 Kg., received 3.55 cc. of air per kilogram of body weight and displayed a moderately severe reaction (fig. 2).

At one minute thirty seconds, respiration became gasping and irregular; at eleven minutes, more regular, and at fifteen minutes, normal.

At two minutes, the injection of air was complete.

At three minutes twenty seconds, the blood pressure, which had begun to rise with the beginning of the injection of air, reached a maximum of 40 mm. of

mercury above normal. It then fell gradually to a minimum of 30 mm. of mercury below normal at twenty-three minutes. It was commencing to rise when the readings were stopped.

The pulse was regular and strong throughout.

Unconsciousness continued, although no more anesthesia was administered. After one hour twitching contractions of the legs and walking movements began. The muscles were spastic and at times the decerebrate posture of Sherrington was assumed. The dog moaned and howled now and then, although obviously unconscious. No cardiorespiratory irregularities were noted. After four hours, consciousness returned sufficiently to permit vague recognition of surroundings and unsteady walking, but this was temporary and death occurred in deep unconsciousness at five hours twenty minutes.

EXPERIMENT 2.—Dog 28, weighing 22 Kg., received 3.9 cc. of air per kilogram of body weight and presented a severe reaction (fig. 3).

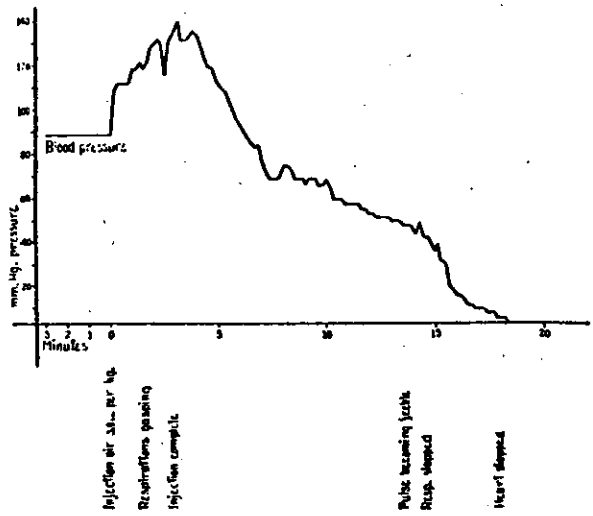

FIG. 3 (dog 28).—Injection of air into the pulmonary vein, with the dog in the horizontal position. Severe reaction.

At two minutes, respirations were gasping. There were periods without breathing. At fifteen minutes, breathing ceased.

At three minutes twenty seconds, the injection of air was complete.

At three minutes ten seconds, the blood pressure, which began to rise with the injection of air, reached a peak of 52 mm. of mercury above normal, and then fell jerkily to 0 at eighteen minutes twenty seconds.

The pulse remained regular and full until the fourteenth minute, when it became increasingly feeble; it ceased at eighteen minutes twenty seconds.

Others of these dogs, receiving smaller doses, showed reactions during the first half hour similar to those of dog 28, but less severe and usually followed by recovery. There was always a period of unconsciousness beyond that to be expected from the anesthetic.

Group *b*: Position Vertical, Head Down, Thirty-Two Dogs: EXPERIMENT 1. —Dog 70, weighing 23.6 Kg., received 1.22 cc. of air per kilogram of body weight and presented a moderately severe reaction (fig. 4).

Respirations were affected at no time.

At one minute, the injection of air was complete.

At ten seconds, the blood pressure rose 20 mm. of mercury, dropped almost immediately and remained about 10 mm. of mercury below normal.

At fourteen minutes, the pulse, thus far regular and strong, suddenly began to skip beats, often two or three together, and blood pressure took wide drops. This irregularity continued twenty minutes and suddenly stopped. The pulse continued normal.

At five minutes, consciousness began to return and ether had to be readministered. At thirty minutes, ether was discontinued and the apparatus disconnected. The dog began to awaken as ordinarily from anesthesia and showed no effects of embolism.

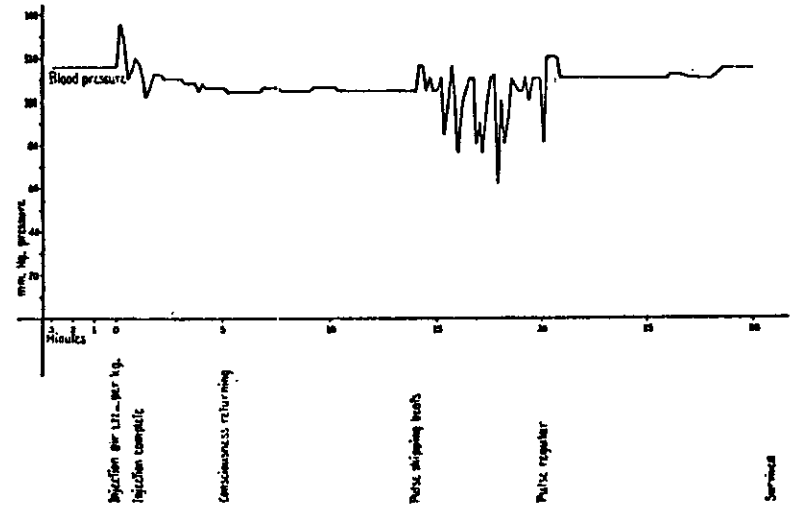

FIG. 4 (dog 70).—Injection of air into the pulmonary vein, with the dog in the head-down position. Moderately severe reaction.

EXPERIMENT 2.—Dog 66, weighing 18.1 Kg., received 1.22 cc. of air per kilogram of body weight and had a severe reaction (fig. 5).

Respirations were normal until the fourteenth minute, when they abruptly failed and represented the last sign of life.

At one minute, the injection of air was complete.

At twenty seconds, the blood pressure was 20 mm. of mercury above normal. It dropped slightly and then rose to a level of from 10 to 15 mm. of mercury above normal. At thirteen minutes, the heart action, which had till then been strong and full, suddenly failed and the blood pressure dropped precipitously to 0 at fourteen minutes.

Dogs in this position showed only cardiovascular symptoms. Heart block was frequent and characteristic and was the cause of death, rather than the gradual myocardial failure seen in the horizontal position.

With large doses, sudden, total block occurred very early; with smaller amounts, total block appeared as abruptly but after from ten to twenty minutes of fairly normal course immediately preceded or not by a few dropped pulse beats, or a period of dropped beats (partial block) came and went without warning, followed by recovery. No heart block was initiated after thirty minutes. In none of the animals were there signs of involvement of the central nervous system. There was no interference with consciousness.

Group *c*: Position Vertical, Head Up, Eighteen Dogs: Dog 48, weighing 9.1 Kg., received 3.9 cc. of air per kilogram of body weight and presented a severe reaction (fig. 6).

At thirty seconds, the respirations were shallow and gasping; they ceased at one minute.

At one minute ten seconds, the injection of air was complete.

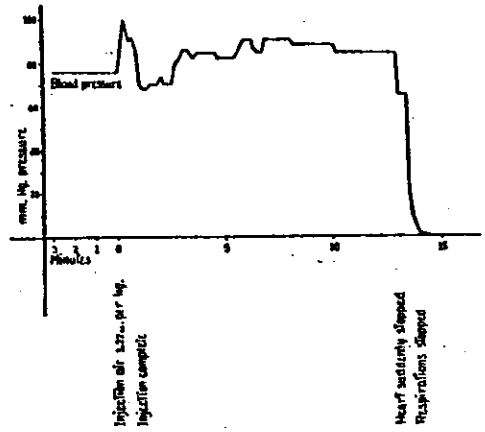

FIG. 5 (dog 66).—Injection of air into the pulmonary vein, with the dog in the head-down position. Severe reaction.

At twenty seconds, the blood pressure had risen to 38 mm. of mercury; it dropped immediately to 0 at four minutes.

At two minutes, the pulse became weak, and the heart action ceased at four minutes as the last sign of life.

Other dogs that received smaller doses exhibited less severe reactions, but none recovered. The respirations were almost instantly affected and permanent cerebral injury with unconsciousness occurred with the smallest doses. The heart showed no disturbance until some time after respirations ceased.

Group d: Investigation of Blood Pressure Reaction, Ten Dogs: The cause of the initial elevation in blood pressure that appears characteristically in air embolism from the pulmonary vein was investigated. Possible causes for this are direct cardiac effects, action on the central nervous system and action directly on the blood vessels. The last

appeared the most likely, for air accumulates in the peripheral arterioles and capillaries and probably increases resistance to blood flow. The first two possibilities were eliminated by experiment, as follows:

With the animals under ether anesthesia, a cannula was inserted in an intercostal artery, pointing toward the aorta. With the dog horizontal, air was injected through the cannula and intercostal vessel into the descending aorta at a rate of 25 cc. per minute. Various doses of air were employed.

Dog 40, weighing 22.4 Kg., received 3.9 cc. of air per kilogram of body weight (fig. 7).

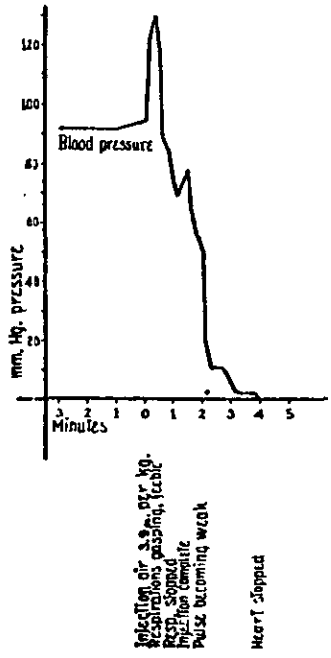

FIG. 6 (dog 48).—Injection of air into the pulmonary vein, with the dog in the head-up position. Severe reaction.

The respirations and pulse were affected at no time.

The blood pressure commenced to rise immediately after the injection was started and reached 40 mm. of mercury above normal at thirty seconds. This elevation was maintained for five minutes, when the pressure returned to normal.

At three minutes thirty seconds, the injection of air was complete.

Autopsy showed no air to have entered the coronary arteries or vessels of the head, neck and forelegs.

Tolerance.—The tolerances for air injected into the circulation at various points were compared:

With the animals under ether anesthesia, the pulmonary vein was cannulated in twenty-one dogs, the jugular vein in twenty-six dogs and

the seventh intercostal artery (descending aorta) in ten. Into each dog was injected an amount of air determined according to the body weight and varied from dog to dog, with the purpose of finding the maximum tolerance dose. The rate of injection was 25 cc. per minute. After four hours the outcome was noted, whether by death or by recovery.

The results are charted in figure 8. Here each of three columns represents the greatest amount of air per kilogram of body weight withstood in one of the forms of air embolism. The figures inserted in each column specify the numbers of dogs used, and the positions of the figures indicate the doses and the fates of the dogs. Thus, the maximum tolerance dose for the pulmonary vein is 1.5 cc. per kilogram, while those for the jugular vein and descending aorta are 76 and 70

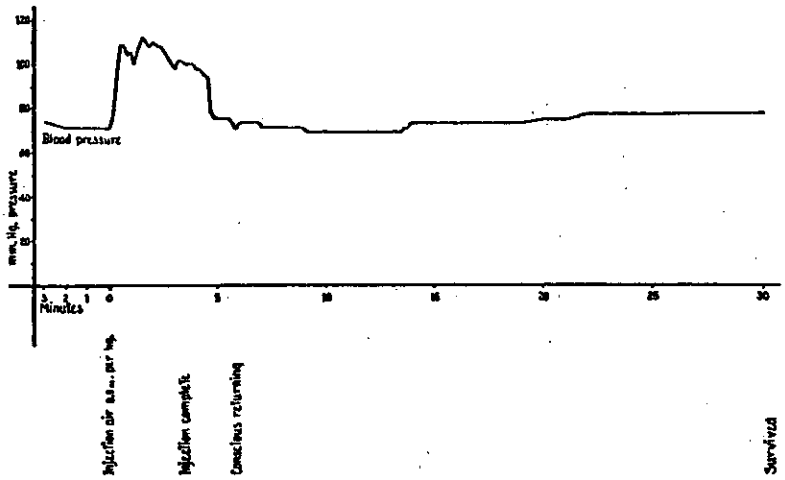

FIG. 7 (dog 40).—Injection of air into the intercostal artery (aorta), with the dog in the horizontal position.

cc., or at least fifty times as great. Considerable individual variation is evident.

The tolerance for air injected into the pulmonary vein was determined for various positions of the body, with twenty-one dogs in the horizontal position, seventeen with the head up and thirty-two with the head down.

The results are charted in figure 9, the same method being employed as for the preceding chart. The maximum tolerance dose is 0.5 cc. per kilogram of body weight with the head up, 1.5 cc. or three times as great in the horizontal position, and 3.3 cc. or six and one half times as great with the head down. Individual variation presents itself.

Cause of Death.—The observations recorded concerning the symptomatology and distribution of the air suggest that the cause of death differed in certain body positions. With the head up, the air ascended

and involved the brain massively. Death resulted either early from respiratory failure (embolism of the medulla oblongata) or, later from decerebration.

In the head-down posture, the air ascended caudally. The coronary arteries were affected most seriously. The heart instantly ceased to beat or, with smaller doses, it continued for a few minutes and then underwent heart block. The brain was protected from embolism and played no part in the cause of death.

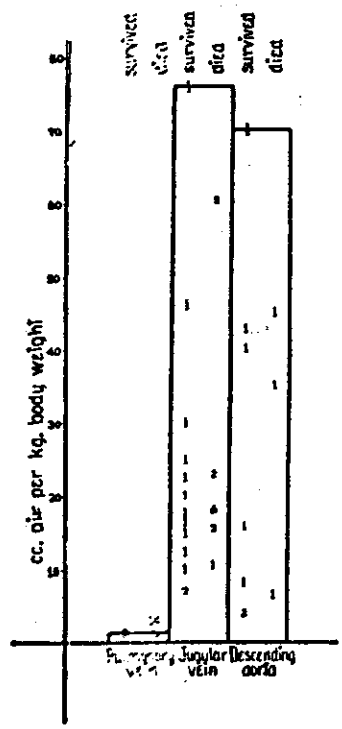

FIG 8.—Tolerance for air injected into the circulation at various points.

In the horizontal position, the air passed to both brain and coronary vessels. In certain instances, the symptoms preceding death suggested involvement of the brain as the lethal factor; in others, coronary involvement. To test the relative importance of these two factors in this position, experiments were devised wherein the brain was protected from air embolism:

With the animals under ether anesthesia, air traps were placed in both carotid arteries. Both vertebral arteries were ligated. A strand of wire was twisted tightly about the neck, including all structures except the carotid arteries, jugular veins, vagus nerves and trachea. Thus, the only blood supply remaining to the brain was through the

trapped carotid vessels. Three and nine-tenths cubic centimeters of air per kilogram of body weight, which is a lethal dose, was then injected into a pulmonary vein. Seven dogs were used.

Dog 32, weighing 11.5 Kg., did not present symptoms referable to embolism. The animal recovered. At one hour, the dog was killed.

Autopsy revealed that the distribution of air was typical of that of pulmonary vein air embolism in this position, except that the head and neck were free. The traps contained 32 cc. of air.

In one other dog, the result was the same. In five dogs, death occurred within a few minutes after embolism.

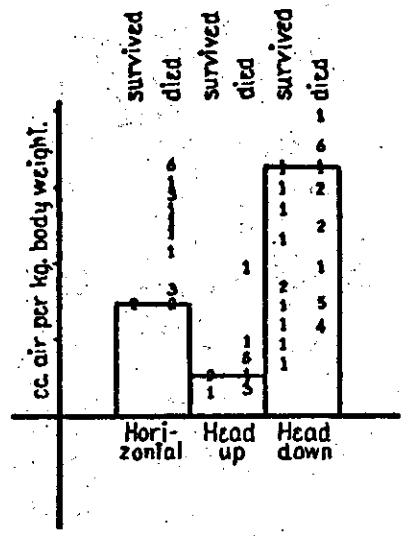

FIG. 9.—Tolerance for air injected into the pulmonary vein in various positions.

DEDUCTIONS

These animals were under general anesthesia at the time of the injection of air, and during the first ten to twenty minutes the symptomatic effects of embolism of the higher brain centers were necessarily eliminated. This part of the picture is supplied, however, in the experiments in the section on etiology.

The symptomatology was found to be similar in all details to that in man, and to be separable into two types, i.e., neuromuscular and cardiovascular. Extreme variation in appearance and degree also occurred, even with the same amounts of embolus.

There were two well defined periods in the reaction, acute and chronic. The acute period lasted up to one-half hour and was characterized by disorders of respiration, heart function and blood pressure, together with irritative and paralytic effects in the higher brain centers.

The chronic period presented states of semidecerebration or total decerebration, delirium, semilucid periods and convulsive seizures. Improvement leading to recovery was seen at any stage but was rare after three hours. The severity of symptoms was in proportion roughly to the amount of embolus; death occurred in either period.

The type of symptoms was determined largely by the position of the animal. In the vertical position, head up, the neuromuscular type was dominant, and the only cardiovascular effect detectable was the elevation of the initial blood pressure. In the vertical position, head down, cardiovascular responses alone appeared. With the dog horizontal, both types occurred and in varying proportions but the neuromuscular usually predominated.

A constant symptom was the elevation of the initial blood pressure. Evidence was obtained that this resulted from the accumulation of air bubbles in the peripheral arterioles and capillaries with increased resistance to arterial blood flow.

The tolerance of the dog for air injected into the circulation depends largely on the portal of entry. In the jugular vein or descending aorta more than fifty times as much may be withstood as in the pulmonary vein. In the pulmonary vein tolerance depends on body position, and is least in the head-up position, three times as great in the horizontal and six and one-half times as great in the head-down position.

The fatal effects of air embolism from the pulmonary vein are due to impairment of three vital functions; i. e., cardiac activity by the obstruction of the coronary arteries, cerebral and medullary function by blockage of the arteries of the brain and blood circulation by blockage of the pulmonary arteries. Either the first or the second may be the primary cause of death; the third is never more than contributory. The first is the sole cause of death when the animal is in the head-down posture and the mechanism is by heart block; the second alone causes death when the animal is situated head up, with respiratory paralysis in the early stage or decerebration later; in the horizontal position all three contribute and the first or the second may be primary, depending on the chance distribution of the air embolus.

DIAGNOSIS AND PROGNOSIS

The diagnosis of air embolism from the pulmonary vein has been made without difficulty when sucking was heard at an open vessel or when gas was injected into the chest immediately before the symptoms. Becker,[32] Stargardt,[33] Perthes[34] and others have been led by the visual

32. Becker, E., quoted from Brauer, L.; Schröder, G., and Blumenfeld, F.: Handbuch der Tuberkulose, ed. 3, Leipzig, J. A. Barth, 1923, vol. 2, p. 461.

33. Stargardt, quoted from Gundermann, W.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. 33:261, 1921.

34. Perthes, quoted from Gundermann, W.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. 33:261, 1921.

disturbances in some of these cases to examine the eyegrounds and were able to establish a diagnosis by seeing bubbles in the retinal vessels. A large proportion of the cases, however, have probably remained obscure from lack of direct evidence. Often the portal of entry of air or gas into the circulation was not apparent, nor was there a sucking sound: no heart murmur occurred to point to the diagnosis, as in air embolism from a peripheral vein; an ophthalmoscope has rarely been at hand.

The symptomatology has not assisted greatly in diagnosis, due to confusion with that of other forms of sudden collapse, i.e., internal hemorrhage, surgical shock, heart failure, the syncope that ensues with the rapid removal of much fluid from the pleural cavity and pleural reflex. The last of these, otherwise known as pleural eclampsia or pleural shock, has contributed chiefly to the confusion, for it is believed by many that nerve impulses elicited from the pleura and lung by trauma from an instrument are capable of producing all symptoms seen in air embolism. The nature of such nerve reflexes has been studied. Brodie and Russell [35] demonstrated strong vagal responses in animals obtained by stimulation of vagal fibers at the hilum, bronchi and alveoli of the lung. Sauerbruch [36] saw sudden heart failure in man immediately following mass ligation at the hilum of the lung or probing within a bronchial fistula. Johnson and Luckhardt [37] found that sudden, forceful inflation of the lungs in man and animals results in vagus reflex that profoundly slows the heart and depresses the blood pressure, often fatally, and Johnson and Van Allen [38] proved that this reflex originates from the vagus fibers in the lung. Moreover, the experimental work of Capps and Lewis [39] indicated the presence of two powerful reflexes, one vagal and resulting in cardiac inhibition and the other vasomotor with dilator influence on the peripheral vessels. These could be obtained separately or at once by irritation of the inflamed but not of the normal pleura. The cardio-inhibitory reflex was in itself insufficient to cause death but the vasomotor effects were frequently not recovered from; both served to lower the blood pressure profoundly. Thus, it is proved that what may be termed pleural reflex exists in both man and animals and that inhibition of the heart rate, peripheral vasodilatation and fall in the blood pressure occur and may result in death. On the other

35. Brodie, T., and Russell, A.: J. Physiol. 26:92, 1900.

36. Sauerbruch, F.: Chirurgie der Brustorgane, Berlin, Julius Springer, 1925, vol. 2, p. 160.

37. Johnson, C. A., and Luckhardt, A. B.: Am. J. Physiol 83:642, 1928; ibid. 84:453, 1928.

38. Johnson, C. A., and Van Allen, C. M.: Unpublished work.

39. Capps, J. A., and Lewis, D. D.: Am. J. M. Sc. 134:868, 1907; Blood-Pressure-Lowering Reflexes from Irrigation of the Chest in Empyema, Arch. Int. Med. 2:166 (Sept.) 1908.

hand, no matter how profound these effects have been, no one has obtained focal irritative and paralytic phenomena of the brain such as occur commonly in cerebral air embolism. In this connection it is to be emphasized that in the lung inflation phenomenon of Johnson and Luckhardt the cerebral symptoms were shown to be the result of ischemia of the brain and without relation to the vagal reflex.[28] Disregarding these facts, two extreme and opposite views are held as to the cause of these obscure cases of sudden collapse following instrumentation of the lung. The majority of authors, as Forlanini,[4] Saugmann[40] and Stivelman,[3] diagnose pleural reflex and pay little or no attention to the possibility of air embolism, while others, notably Brauer,[38] Wever[39] and Schlaepfer,[37] as consistently ascribe the condition to air embolism.

All characteristic symptoms that have been noted in this form of air embolism failed when the subject was under general anesthesia or when the air entered rapidly and in large amounts, since no opportunity was given for evidence of involvement of the brain. The picture was simply that of sudden heart and respiratory failure.

The diagnosis made at autopsy of air embolism from the pulmonary vein has depended on the demonstration of air in the blood stream or of typical cerebral lesions. Both of these could not appear in the same body, since air remains in the vessels during life a few minutes or hours only and the degenerative changes in the brain from embolism develop only after fifteen hours.[30] Thus, patients in whom death occurs between two and fifteen hours after the onset of symptoms are expected not to exhibit at autopsy evidence of air embolism, either in the form of intravascular air or that of secondary changes in the brain. Moreover, very small amounts of air may be lethal in embolism from the pulmonary vein, and even though death occurs at once its demonstration in the peripheral vessels is difficult. Use of the roentgen rays has been proposed for diagnosis.[41]

Richter[42] described a technic for the demonstration of air or gas in the vessels at death which has become standard. Each organ is isolated in situ by ligation of the vessel supply, then removed and incised under water. Air escaping from the tissues bubbles up plainly. The heart is managed somewhat more simply, for ligation and removal is dispensed with. The pericardium is opened and held suspended to serve as the dish for water submersion. Objection has been raised to this method as laborious and misleading, for the air may be withheld in the vessels by clots and fail to bubble forth, and the water quickly

40. Saugmann, C.: Beitr. z. Klin. d. Tuberk. **31**:571, 1914.

41. Baum, F.: Am. Med. **33**:271, 1927.

42. Richter, M.: Gerichtsärztliche Diagnostik und Technik, Leipzig, S. Hirzel, 1905.

becomes bloody and obscures the tissues. Moreover, direct observation of the vessels serves to detect even very small amounts of air, since the smaller arterioles are translucent enough to show air bubbles distinctly and the air in larger vessels, heart, cavae and aorta, is present in the form of froth and escapes as such plainly when the lumen is opened.

It is well known that little significance can be placed on finding air bubbles in the cerebral vessels at autopsy, unless great care has been taken in exposing the brain. In lifting off the skull cap, as it is routinely carried out, cortical vessels are stretched and ruptured and air is sucked from the atmosphere into their lumina.

Differentiation at autopsy of the type of air embolism has depended on three things. 1. The vessel that served as portal of entry is sought. 2. The distribution of the air is determined, the fact being borne in mind that the lesser circulation acts as an effectual barrier to air bubbles. Thus, if air was found in the left side of the heart or the peripheral arteries, the case was one of embolism from the pulmonary vein; if only in the large veins, right side of the heart and pulmonary arteries, it was embolism from a peripheral vein. One exception has pertained to this; a patent foramen ovale may allow air to pass from the right to the left side of the heart and differentiation is prevented. 3. The typical cerebral degenerative lesions are sought for and indicate the pulmonary vein type of embolism, unless there is a patent foramen ovale.

It has been emphasized that fallacious conclusions may result from the presence of putrefactive gases in the blood at autopsy. Dyrenfurth [43] found by actual measurement that within twenty-four hours amounts of gas up to 0.25 cc. may be present in the heart cavity, and that this may increase during the next few days to 4 cc. In air embolism from a peripheral vein there was regularly as much as 7 cc., but this is probably too high for embolism from the pulmonary vein, where smaller amounts are lethal. Dyrenfurth [44] devised a method for the qualitative test of these gases, to rule out the putrefactive. Simmonds [45] recommended culture of the heart blood for the presence of gas-forming organisms, for the same purpose.

Prognosis has been uncertain. Usually, the return of consciousness has indicated improvement leading to recovery, but in some cases consciousness has been recovered only for relapse to occur. In recovery after pronounced symptoms, focal paralyses lasting as long as six months have been seen.[46]

43. Dyrenfurth, F.: Med. Klin. **22**:807, 1926.

44. Dyrenfurth, F.: Deutsche Ztschr. f. d. ges. gerichtl. Med. **8**:727, 1926.

45. Simmonds, M.: München. med. Wchnschr. **62**:662, 1915.

46. Head, J.: *Personal communication to the authors.*

EXPERIMENTAL WORK

Diagnosis.—A characteristic sign of air embolism from the pulmonary vein, noted practically always in these experiments, was immediate elevation of the arterial blood pressure. The most frequent degree of rise was from 30 to 40 mm. of mercury, but often the initial pressure was more than doubled. The elevation was maintained as long as air continued to be injected and usually also for a minute or two afterward. Even exceedingly small amounts of air produced detectable hypertension. In air embolism from the peripheral vein, on the other hand, initial depression of the blood pressure is the rule. These opposite effects are illustrated in the following experiment.

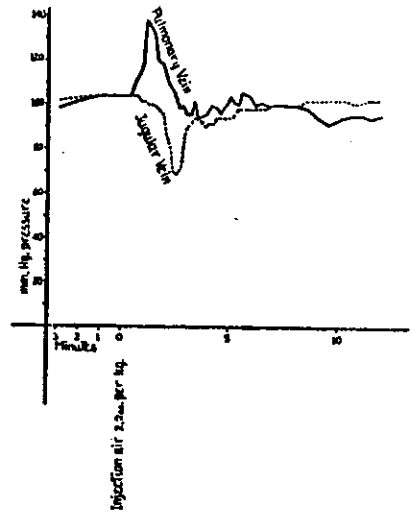

FIG. 10 (dog 6).—Injection of air into the pulmonary vein, followed in thirty minutes by the injection of air into the jugular vein (graphs superimposed).

Dog 6, weighing 8.4 Kg., was fitted with cannulas in both pulmonary and jugular veins. The femoral artery was connected to a mercury manometer and the normal blood pressure level was recorded. Then a small amount of air (2.2 cc. per kilogram) was injected into the pulmonary vein and the blood pressure reaction noted. Forty-five minutes later, when the pressure was again at a normal level, the same amount was injected into the jugular vein, and the reaction again noted.

The two blood pressure curves thus obtained are compared in figure 10 by superimposition. One is seen to be the reverse of the other.

A second characteristic sign of air embolism from the pulmonary vein is elicited as follows: A stab cut is made through the skin of a part of the body that is uppermost and bleeding is produced. Bubbles of air will stream out distinctly with the blood. The test should be made within fifteen minutes after embolism.

Prognosis.—Prognosis in air embolism from the pulmonary vein in the dog was possible within certain limits: 1. The severity of the symptoms depended in general on the amount of air entering the circulation. 2. Primary respiratory failure was looked for only within the first ten to fifteen minutes; primary heart failure, within half an hour. 3. Unconsciousness, when continued longer than half an hour, indicated serious cerebral involvement.

CLINICAL CASES

Case 2 illustrates the use of the blood pressure reaction in the diagnosis of air embolism in man.

CASE 2.—A white woman, aged 51, presented an illness of seven months' duration. The onset was sudden, with chills, fever and pain in the left side of the chest. Cough developed and fever continued for three weeks. There had been continuous cough and intermittent periods of fever since then. There was 250 cc. of foul sputum daily, which was negative for tubercle bacillus. A moderate loss of weight and strength occurred. The diagnosis was chronic abscess of the left lung.

The patient was admitted to University of Iowa Hospital, surgical service. Iodization of the bronchial tree showed a large filling in the center of the left lung, extending laterally to within 2 cm. of the pleura. This was interpreted as an abscess cavity.

On two occasions attempts were made to reach the abscess with an exploratory needle, without success. The third attempt was as follows: With the patient under local anesthesia, the third rib was resected in the anterior axillary line, which was a point shown by fluoroscopy to overly the abscess closely. The pleura was found free, and the wound was packed with gauze to produce adhesions. Four days later, the pack was removed and exploration was performed without anesthesia, the patient sitting semi-erect. A large hypodermic needle, attached to a syringe, was passed perpendicularly through the rib bed into the lung. The parenchyma was found to be tough. Nothing could be aspirated, except that at one point blood was freely drawn and at another air. The puncture was repeated, and at a depth of 5 cm. the patient started to cough. The needle was withdrawn. She raised a little bright frothy blood and continued to cough urgently. She experienced a prickling sensation over the body surface and became unable to speak. Dyspnea developed and, at about one minute, unconsciousness. The pulse rate was 66, and was slightly irregular. The color was somewhat cyanotic. At about ten minutes (accurate time is not kept at such emergencies) the blood pressure was taken and found to be 180 systolic and 80 diastolic; at twenty minutes, 162 systolic and 76 diastolic; at thirty minutes, 152 systolic and 70 diastolic; at forty minutes, 140 systolic and 68 diastolic; at fifty minutes, 130 systolic and 65 diastolic, and seventy-five minutes, 125 systolic and 65 diastolic. Consciousness returned at thirty minutes and with it speech; at this time it was noted that the entire left side of the body was paralyzed and with hyperactive tendon reflexes. There was no anesthesia. The eyegrounds were normal. At forty-five minutes, the paralysis began to disappear and cleared at one hour. A sensation of heaviness persisted in that side of the body. Dyspnea gradually disappeared. After one and one-half hours the condition was normal, except for the pulse rate, which was 120.

It was thought that air embolism from the pulmonary vein was the cause of the condition, since: 1. Needle puncture in a sclerotic lung is known (case 1) to be capable of producing a bronchovenous fistula, and such a communication permits air to be inspired into the circulation. Here a bronchus and blood vessel are known to have been pierced in a sclerotic lung. 2. During the height of the reaction the blood pressure was found markedly elevated, and in no other form of sudden collapse, save cerebral hemorrhage, is this seen. 3. The symptoms were chiefly those of transient cerebral dysfunction characteristic of air embolism of the brain.

DEDUCTIONS

The diagnosis of air embolism from the pulmonary vein is assisted by two phenomena, readily elicited:

1. Initial elevation of the blood pressure: In the dog, this lasts as long as air continues to enter the circulation and heart action is maintained. Even very small amounts of air produce noticeable elevation. In man, the reaction is described, and here the elevation was maintained about one hour. The presence of this phenomenon in cases of sudden collapse with instrumentation of the lung rules out air embolism from a peripheral vein, pleural and vagal reflex, hemorrhage and traumatic shock. Its transiency rules out cerebral hemorrhage.

2. "Air bleeding": In air embolism from the pulmonary vein, the peripheral capillaries in the upper parts of the body contain bubbles of air, and these flow plainly out with the blood from a wound. A small stab incision serves to demonstrate this. The phenomenon is pathognomonic.

Prognosis is difficult; it depends on appreciation of the amount of air embolus, severity of symptoms and the time interval.

PREVENTION

Measures to insure against air or gas embolism during the administration of artificial pneumothora, particularly at the initial filling, have eliminated much of the danger. Thus, there is the incision method of Brauer,[47] employment of a blunt needle, manometer control, etc. The accident occasionally takes place, however, even in the best hands.

During the irrigation and probing of pleural fistulas, it has been advocated [48] that no injury, either by direct trauma or by stretching, be inflicted on the pleural surface or pleural adhesions. Instances of shock following such procedures have been accompanied by bleeding as evidence of damage to vessels within the sinus.

47. Brauer, L., and Spengler, L.: Beitr. z. Klin. d. Tuberk. **14**:419, 1909.

48. Schlaepfer, K.: Surg. Gynec. Obst. **37**:510, 1923.

Spontaneous suction by a pulmonary (or other) vein of air from the outer atmosphere is prevented with certainty by causing the patient to breathe under positive pressure at the time, as demonstrated by Tiegel in 1907.[49] The principle of the apparatus necessary for this purpose is illustrated in figure 11.

EXPERIMENTAL WORK

Various measures that might be expected to prevent spontaneous air embolism from the pulmonary vein were tested in the dog, (1) under the conditions of external venous fistula and (2) under conditions of bronchovenous fistula.

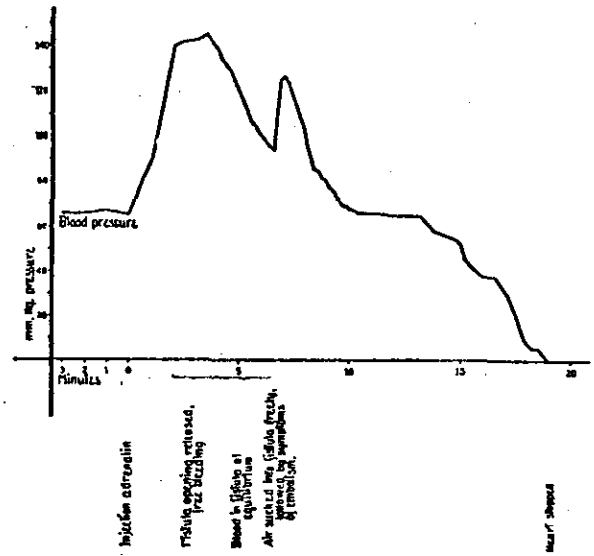

FIG. 11 (dog 50).—Pulmonary vein fistula; temporary protection against air suction by the injection of epinephrine.

External Fistula.—(*a*) Positive Pressure Breathing, Two Dogs: Dog 49, weighing 8.5 Kg., was anesthetized and fitted with a pulmonary vein cannula. Placed in the horizontal position, positive pressure breathing was applied.

At 20 cm. of water pressure, the cannula was opened. The blood from the vein flowed freely out, both in inspiration and in expiration.

At 17 cm. of water pressure, the bleeding was less free.

At 14 cm. of water pressure, bleeding occurred during expiration, and the column of fluid in the cannula remained stationary in inspiration. At 11 cm., the column of fluid was stationary in expiration and dropped toward the vein slightly in inspiration.

At 8 cm., the fluid meniscus appeared above the surface of the chest in expiration and dropped below in inspiration.

At 5 cm., the fluid remained always below the surface of the chest but embolism did not occur.

49. Tiegel, M.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **3**:789, 1907.

At 3 cm., air was drawn freely through the cannula, and the animal died of air embolism.

(*b*) Intravenous Injection of Epinephrine, Four Dogs: Dog 50, weighing 5.8 Kg., was placed under general anesthesia, in the horizontal position, and was fitted with a pulmonary vein cannula and a femoral blood pressure recording apparatus. The normal pressure was recorded, and then 0.5 cc. of epinephrine hydrochloride was injected intravenously (fig. 11).

At injection, the blood pressure started to rise.

At two minutes, when the pressure was 74 mm. of mercury above normal, the cannula was opened and found to bleed freely.

The pressure continued to rise and then fell gradually with constant tendency to bleed from the cannula.

At four minutes ten seconds, when the pressure was 72 mm. of mercury above normal, equilibrium was reached. As the pressure fell further the meniscus in

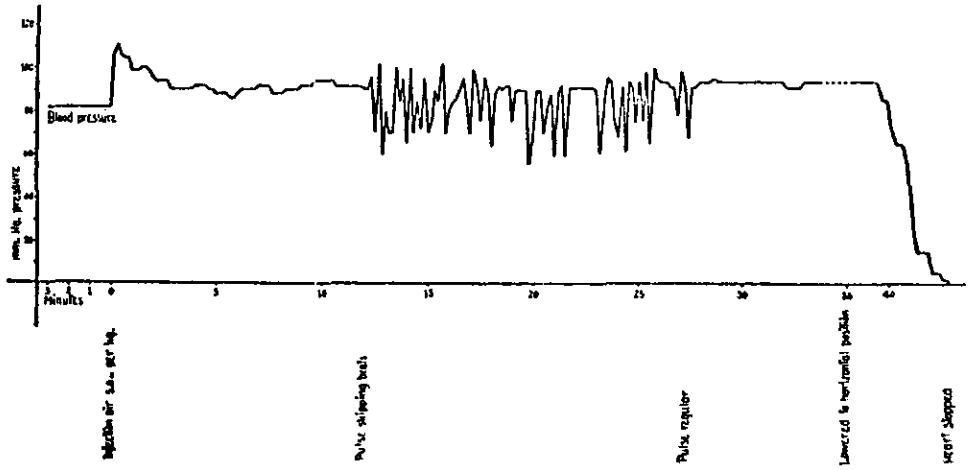

FIG. 12 (dog 111).—Injection of air into the pulmonary vein, with the dog in the head-down position. Illustrating the fatal effect of resuming the horizontal position too soon.

the cannula dropped, and at six minutes thirty seconds, at 28 mm. of mercury elevation, there was sucking of air into the vein, and the dog died from embolism.

In other dogs, the effect was similar, although the blood pressure values were different in each case. Ephedrine was found to act in the same manner.

Bronchovenous Fistula.—(*a*) Positive Pressure Breathing, One Dog: In dog 51, weighing 6.9 Kg., while under general anesthesia, a bronchovenous fistula was created as in dog 1 (section on etiology) and the communication was kept blocked at first by clamping the U-tube. Positive pressure breathing was applied. At 10 cm. of water pressure, the clamp was removed and patency of the fistula was established. Air passed immediately from bronchus to vein, and the dog died.

(*b*) Negative Pressure Breathing, One Dog: Dog 52, weighing 7.5 Kg., was treated in a similar manner to dog 51, except that negative pressure breathing

was administered. At 24 cm. of water pressure, the clamp was removed from the U-tube. Air passed rapidly from the bronchus to the vein. The dog died.

(*c*) Intravenous Injection of Epinephrine, Three Dogs: Dog 53, weighing 9.2 Kg., was fitted with a bronchovenous cannula and a femoral blood pressure recording apparatus. The normal pressure was determined and then 0.5 cc. of epinephrine hydrochloride was injected intravenously.

At injection, the blood pressure began to rise.

After one minute and fifty seconds, with the pressure 56 mm. of mercury above normal, the U-tube was released. The venous blood flowed quickly toward the bronchus.

The pressure continued to rise and then fell gradually, with a constant tendency to bleed from the vein.

After four minutes, the pressure reached 14 mm. of mercury above normal and air was drawn with each inspiration from bronchus to vein, with death.

A similar, transient protection against embolism was seen in the other dogs.

Bronchus Block, Three Dogs: Dog 54, weighing 10 Kg., was fitted with a bronchovenous cannula. A small rubber bag connected with a rubber tube was introduced by bronchoscope into the primary bronchus on the side of the cannula. By inflating the bag suddenly during expiration, the bronchus was blocked and a negative pressure established in the peripheral bronchi in inspiration.

The bronchovenous cannula was released; no air passed into the vein. The bronchus block was released; fatal air embolism immediately took place.

A similar result was seen in the other dogs.

DEDUCTIONS

Spontaneous air embolism from an external fistula of the pulmonary vein was prevented in dogs by two means: (1) Positive pressure breathing (Tiegel), with pressure as low as 5 cm. of water; pressures above 14 cm. of water caused the vein to bleed. (2) The intravenous injection of epinephrine or ephedrine; the protection lasted only while the blood pressure remained above certain levels, which was only a few minutes. Accompanying this was a tendency to bleed from the vein.

Spontaneous embolism from a bronchovenous fistula in dogs was prevented by two means: (1) The intravenous injection of epinephrine or ephedrine; the effects were the same as in external fistula. (2) Bronchial block; protection lasted as long as the block was maintained, and without tendency to bleed from the vein. The use of positive pressure or negative pressure breathing afforded no protection but rather encouraged embolism.

TREATMENT

Consistent benefit in air embolism from the pulmonary vein has not been obtained experimentally or clinically by any form of treatment. Cardiorespiratory stimulants and intracardiac injections of epinephrine

have had no effect. Gundermann[19] exposed the heart in dogs and aspirated and massaged the ventricle but could not rescue any one. He explained his failure by indicating the cause of heart failure as myocardial ischemia, necessarily resistant to any artificial stimulant short of reestablishment of the coronary circulation. Reyer and Kohl[50] suggested that the person's head be lowered after embolism, in order to bring additional blood to the brain, but this has not proved of assistance.

EXPERIMENTAL WORK

Two measures appeared of likely value in treatment, as indicated by the aforementioned experimental observations, i.e., artificial respiration and the use of the head-down position preliminary to air embolism.

Artificial Respiration, Seven Dogs.—These experiments were carried out in the following manner:

Each dog was placed under general anesthesia in the horizontal position, and a pulmonary vein cannula was inserted. Continuous intratracheal insufflation of air, according to the original principle of Meltzer and Auer,[51] was instituted, and then a measured dose of air was injected into the pulmonary vein at a rate of 25 cc. per minute. The outcome was noted, whether by death or by recovery at four hours. The amounts of air were varied, to determine the maximum tolerance dose.

The maximum tolerance dose was 1.5 cc. per kilogram, which is the same as that found without artificial respiration in this position.

Vertical Position, Head Down, Thirty-two Dogs.—Experiments have been described in the section on tolerance (fig. 9) which indicate that, when the dog is in a vertical position, head down, the maximum tolerance dose is 3.3 cc. per kilogram of body weight, or two times that in the horizontal position.

Vertical Position, Head Down, Plus Artificial Respiration, Fifteen Dogs.—The artificial respiration was combined with the head-down position, described in the two previous experiments. The maximum tolerance dose for air injected into the pulmonary vein was found to be 5 cc. per kilogram of body weight or 50 per cent greater than with the head-down position alone.

This increased tolerance to air embolism was obtained only when artificial respiration was maintained at least one-half hour and when the position was held for one hour or more. The latter requirement is emphasized by experiment:

Dog 111, weighing 12 Kg., under general anesthesia, was placed in a head-down position and given 5 cc. of air per kilogram of body weight into the pulmonary vein, and the reaction was noted (fig. 12).

At thirty-eight minutes, recovery from the embolism seemed complete. The anesthetic had been discontinued and the dog had regained consciousness. The

50. Reyer, G. W., and Kohl, H. W.: Air Embolism Complicating Thoracic Surgery, J. A. M. A. 87:1626 (Nov. 13) 1926.

51. Meltzer, S., and Auer, J.: J. Exper. Med. 11:622, 1909.

table was lowered to the horizontal position. Immediately, the blood pressure rose slightly and then dropped steadily to 0 at forty-seven minutes.

At autopsy, it was found that air that had accumulated in the large trunk and the arteries of the hind legs had passed backward against the blood stream, ascended the aorta and reached the branches leading to the head and the coronary arteries. This retrograde embolism had obviously occurred at the time of change of the animal's position.

This occurrence of retrograde embolism on change of body position was demonstrated in two other dogs by means of air traps inserted in various vessels.

DEDUCTIONS

Treatment for air embolism from the pulmonary vein by artificial respiration (intratracheal insufflation of Meltzer and Auer) is of assistance only when the animal has been placed in a steep, head-down position before the onset of embolism. The tolerance for air embolus

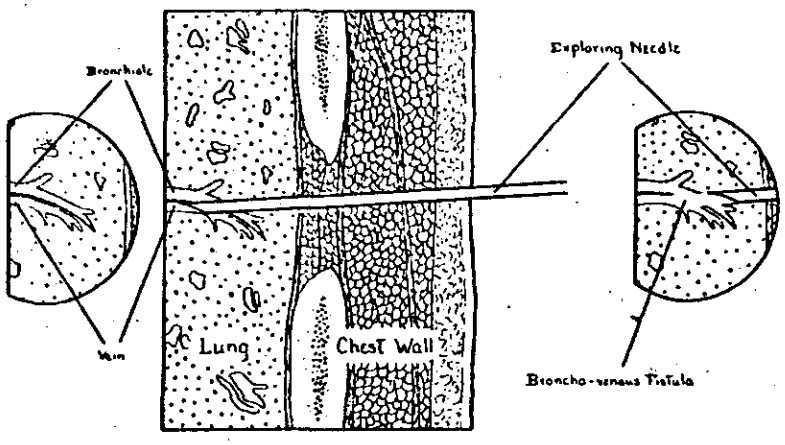

FIG. 13.—Cross-section of the thoracic wall and underlying lung with exploring needle in place. Illustrating the mode of formation of a bronchovenous fistula by needle puncture.

is then 5 cc. per kilogram of body weight, which is distinctly greater than under any other circumstances tested and is ten times as great as in the most susceptible circumstance, i.e., with the head up.

Artificial respiration must be continued for half an hour and the head-down posture for one hour in order to obtain the beneficial effects.

COMMENT

Air embolism from bronchovenous fistula is a complication demanding consideration in exploratory needle puncture of the lung, judging from the evidence of cases 1 and 2. In the parenchyma of the lungs the pulmonary veins lie in close proximity to bronchi, and transfixion of both vein and accompanying bronchus by the needle leaves defects in their walls at adjacent points (fig. 13). If, then, the parenchyma is

consolidated and inelastic, as it frequently is when such exploration is made, the pathway may remain temporarily patent. Likewise, a bronchovenous fistula may form readily in the case of a pulmonary cavity containing a vein in its wall, where a tangential needle thrust could tear the thin partition separating the lumen of the vein from the cavity. Given a patent bronchovenous communication, the vein becomes a branch of the bronchial tree and receives air during inspiration as voluminously as does any bronchial branch of like caliber. Here the person literally breathes into his circulation. The autopsy in case 1 revealed hundreds of cubic centimeters of air in the blood vessels. Such a mechanism may account for many of the obscure instances of sudden collapse following thoracentesis.

The extreme points of view commonly held as to the cause of these obscure complications following lung instrumentation, ascribing it entirely either to air embolism or to pleural reflex, are not justified by the available clinical and experimental evidence. That both entities exist as such and may occur in man and animals is established beyond reasonable doubt, as we have outlined, and differentiation must be made in diagnosing each case. Symptoms of irritation or paralysis of the higher brain centers point to embolism, but in the presence of cardiovascular symptoms alone either of the causes may be in play.

Differential diagnosis is assisted greatly by examination for one or both of two phenomena, i.e., sudden blood pressure alteration and "air bleeding." Marked depression of the blood pressure is seen in pleural reflex and other forms of shock, while elevation is characteristic of air embolism from the pulmonary veins. "Air bleeding" is, of course, pathognomonic of the latter. These signs are obtainable with instruments usually at hand and with no unusual amount of skill.

Air embolism from the pulmonary vein in its various forms is preventable. When there is a possibility of embolism occurring from external fistula of the vein, the use of positive pressure breathing may be relied on to eliminate the negative intrathoracic pressure and the capacity of the thoracic veins for suction. The Tiegel method (fig. 14) is perhaps the best, being simple and well tolerated by the conscious patient. Its principal advantage over other apparatus of the sort is the freely open breathing outlet, for submergence under water is used to procure pressure and there is no choking sensation produced as occurs with the spring valve devices, which elevate the pressure within the mask by obstruction to the outlet. Moreover, the water submersion principle sets the pressure desired and insures against accidental overdistention of the lungs. The pressure used is slight, from 8 to 10 cm. of water.

When there is a possibility of embolism from bronchovenous fistula, certain and controllable means of prevention are obtained only by

blocking the bronchus leading to the affected lung during the operation. The technic for this in man has not been developed but should be comparatively simple and without necessity of bronchoscopy. A fine catheter fitted at the end with a small rubber bag may be passed through the anesthetized larynx and into the bronchus under fluroscopic control, as in the Iglauer [52] method for iodization. The use of epinephrine to raise the pulmonary intravenous pressure prevents spontaneous suction by the veins but the effect is too transient to be practicable.

The treatment for air embolism is of little avail. The embolized vital centers cannot be well reached by medication and there is no way of removing the air lodged in the vessels. Anoxemia may be prevented and distinct benefit obtained by the use of artificial respiration, as carried

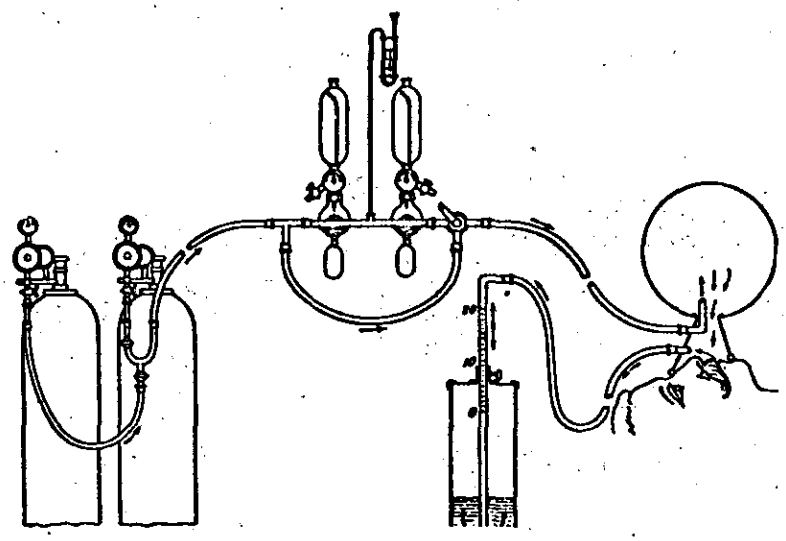

FIG. 14.—Positive pressure breathing apparatus applied to man, according to Tiegel. The air is supplied by tanks to the breathing mask and bag, and the exhaust air is carried out by a tube under water. The depth of the outlet under water determines the pressure breathed.

out in the experiments reported; this is not applicable to clinical experience, as only the principle of continuous intratracheal insufflation is desirable. Any procedure for administering artificial respiration which entails increasing the chest movements is likely to add to the air embolism and should be avoided. Once air embolism has occurred, it is of no benefit to institute the Trendelenberg position. The patient should be allowed to lie in the original position quietly and fight his own battle.

52. Iglauer, S.: Injected Iodized Oil in Roentgen-Ray Diagnoses of Laryngeal, Tracheal and Broncho-Pulmonary Conditions, J. A. M. A. 86:1897 (June

When an operation is contemplated in which there is a possibility of air embolism occurring and when certain means of prevention are not at hand the following procedure is advocated:

During the stage of the operation in which embolism is likely to occur, the patient is placed in a steep Trendelenberg position. The blood pressure is taken every minute or so, to warn of complications and indicate immediate interruption of the operation. If a sudden, marked elevation points to embolism, the diagnosis may be confirmed by eliciting "air bleeding," and the patient must then be maintained in the head-down posture for about two hours, to obviate shifting of the air to other parts of the body (coronary and cerebral vessels). Oxygen may be administered with a tent or other efficient passive methods.

SUMMARY

The subject of air embolism from the pulmonary vein is considered in this paper as to etiology, distribution of the air in the circulation, physiologic reaction, tolerance, cause of death, diagnosis, prognosis, prevention and treatment. Under each of these captions is given a review of the present knowledge and original clinical and experimental observations and deductions.

Particular emphasis is placed on the following conclusions:

1. Bronchovenous fistula may be produced by simple thoracentesis and may form a portal of entry for air into the pulmonary veins.

2. Gravity is a determining factor distributing air in the blood circulation.

3. Embolism of the heart (coronary) and brain are the vital effects. The position of the animal determines which of these are primary in a given case.

4. Tolerance for embolism is greatest when the head of the animal is well depressed and least with the head up.

5. Diagnosis is aided by two characteristic and easily elicited signs, i.e., elevation of the initial blood pressure and "air bleeding."

6. Prevention is certain by employing positive pressure breathing, when an external venous fistula is present, or by bronchial block, when a bronchovenous fistula exists.

7. Treatment, although effective under ideal circumstances, is not practical.

EVALUATION OF THE RAPID RECOMPRESSION-HIGH PRESSURE OGYGENATION APPROACH TO THE TREATMENT OF TRAUMATIC CEREBRAL EMBOLISM

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SUBMARINE MEDICAL RESEARCH LABORATORY
U. S. NAVAL SUBMARINE MEDICAL CENTER REPORT NO. 519
Bureau of Medicine and Surgery, Navy Department
Research Work Unit MR005.04-0057.01

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UNCLASSIFIED

Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY *(Corporate author)*

U.S. NAVAL SUBMARINE MEDICAL CENTER, Submarine Medical Research Laboratory

2a. REPORT SECURITY CLASSIFICATION

UNCLASSIFIED

2b. GROUP

N/A

3. REPORT TITLE

EVALUATION OF THE RAPID RECOMPRESSION-HIGH PRESSURE OXYGENATION APPROACH TO THE TREATMENT OF TRAUMATIC CEREBRAL EMBOLISM

4. DESCRIPTIVE NOTES *(Type of report and inclusive dates)*

Interim

5. AUTHOR(S) *(First name, middle initial, last name)*

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6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
25 March 1968		5

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
b. PROJECT NO. MR005.04-0057.01	SMC, SMRL Report Number 519
c.	9b. OTHER REPORT NO(S) *(Any other numbers that may be assigned this report)*
d.	

10. DISTRIBUTION STATEMENT

This document has been approved for public release and sale; its distribution is unlimited.

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
	U.S. Naval Submarine Medical Center Box 600, Naval Submarine Base New London Groton, Connecticut 06340

13. ABSTRACT

This study compared the conventional Navy recompression treatment tables and the newer rapid recompression-high pressure oxygenation (RR-HPO) method for the treatment of traumatic cerebral air embolism. Seven cases are presented. These cases occurred as a result of submarine escape training at the Naval Submarine Base, Groton, Connecticut, and were successfully treated with the latter method. Factors regarding the rationale of the use of this new approach are discussed. Since the writing of this paper, the Navy Department has approved the treatment schedules recommended herein for the treatment of traumatic air embolism.

DD FORM 1 NOV 65 1473 (PAGE 1)

S/N 0101-807-6801

UNCLASSIFIED

Security Classification

JND PPSO 13152

14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Traumatic air embolism, treatment of						
RR-HPO (Rapid Recompression-High Pressure Oxygen) treatment for air embolism						
Diving - recompression techniques						
Submarine escape						

SUMMARY PAGE

THE PROBLEM

To compare the conventional Standard Navy Recompression Treatment Tables with the newer rapid recompression-high pressure oxygenation (RR-HPO) method for the treatment of traumatic cerebral air embolism.

FINDINGS

Seven cases occurring during the course of submarine escape training at the Escape Training Tank, Naval Submarine Base, Groton, Connecticut, and successfully treated with the newer method are presented. Discussion is presented of the treatment of traumatic cerebral air embolism by both Standard Tables and the newer approach. Factors regarding the rationale of the use of the new approach are given.

APPLICATIONS

It is expected that the Navy Department will approve the treatment schedules recommended in this report for the treatment of traumatic air embolism.

ADMINISTRATIVE INFORMATION

The authors conducted this investigation while both were attached to the Submarine Medical Center, during 1967, as a part of Bureau of Medicine and Surgery Research Work Unit MR005.04-0057. It is Report No. 1 on that Work Unit; however, a related report was published as SMRL Report No. 500, August 1967, under MR005.04-0055.10. The present report was approved for publication on 25 March 1968, and designated as SMRL Report No. 519.

PUBLISHED BY THE SUBMARINE MEDICAL CENTER

ABSTRACT

Comparison of the Navy conventional recompression treatment tables and the newer rapid recompression-high pressure oxygenation (RR-HPO) method for the treatment of traumatic cerebral air embolism is made. The embolism cases treated were incurred during submarine escape training at the Naval Submarine Base, New London, Connecticut. In view of its theoretical and proven practical superiority, the RR-HPO approach described here and in Navy Recompression Tables V-a and VI-a is recommended for the treatment of traumatic air embolism.

EVALUATION OF THE RAPID RECOMPRESSION-HIGH PRESSURE OGYGENATION APPROACH TO THE TREATMENT OF TRAUMATIC CEREBRAL EMBOLISM

INTRODUCTION

Cerebral air embolism may result from any condition in which a gas or mixture of gases enters the systemic circulation, ultimately becoming lodged in small cerebral vessels and occluding the blood supply distally. The treatment for this true medical emergency is prompt recompression. This paper will discuss cases occurring as a result of training in escape from submarines, which were treated by both conventional U. S. Navy recompression treatment tables and the recently developed rapid recompression-high pressure oxygenation treatment tables (RR-HPO), utilizing a considerably shorter treatment time and intermittent oxygen breathing beginning at 2.8 atmospheres absolute. In this series the embolism resulted from overexpansion and rupture of alveoli with the release of air into the pulmonary venous circulation, left heart, aorta and ultimately the cerebral circulation.

DESCRIPTION OF ESCAPE TRAINING

At the Naval Submarine Medical Center, Naval Submarine Base, New London, Connecticut, the air embolism cases seen are coincident to training in submarine escape techniques taking place in the Escape Training Tank. At the present there are two methods of submarine escape being taught, the buoyant ascent method and the free-breathing, buoyant ascent method.

In buoyant ascent training the candidates are placed in a pressure lock located fifty feet below the surface of the water and opening into the side of the tank by means of a door. The lock is then partially filled with water to the level of the top of the door leading into the main tank and then pressurized to the ambient pressure, exerted by the water column at that level. Following pressurization the door may then be opened, allowing free access between the tank and the lock. The trainees take a deep breath of the pressurized air, step through the door into the tank, commence a steady controlled exhalation, and assisted by an inflated life jacket, make a rapid ascent. They travel the fifty feet at 375 feet per minute in seven to eight seconds, continuously and positively exhaling during the ascent to the surface. Since its initiation in 1956, there have been over 128,000 successful buoyant ascent runs.

In the free breathing, buoyant ascent method the trainee also makes an escape from the fifty foot level, entering the tank from the lock and ascending to the surface. The difference is the utilization of a more sophisticated escape appliance in this procedure. The appliance, called the "Steinke Hood" after its inventor, CDR H. E. Steinke, USN, is constructed with a head hood attached to the collar of an inflatable life jacket. During ascent the expanding air from the jacket is vented through two relief valves into the hood expanded and allowing the escapee to inhale if necessary. To ensure the steady and timely decrease of the expanding volume of air in the lungs, the trainees are instructed to shout "ho-ho-ho" in quick succession between each shallow inhalation while ascending. With the additional buoyance of the air filled hood, the trainee travels somewhat more rapidly, approximately 425 feet per minute. Approximately 45,000 successful hood runs have been made since the institution of this mode of training in 1963.

Embolization occurs in those instances in which the intra-pulmonary pressure is not reduced with the concommitant reduction of the intra-pleural and intra-arterial pressures. The latter pressure decreases with the reduction of hydrostatic pressure on ascent. Schaefer found that embolization into the pulmonary veins occurs in dogs when the transpulmonic pressure, (the difference between the intra-pulmonary and the intra-pleural pressure) exceeds 50-70mm. Hg.[1] Such a pressure differential can be developed merely by breath-holding after inhaling air pressurized to three feet of water pressure and ascending to the surface.

DESCRIPTION OF TREATMENT

In the period covered by this report from

1956 through mid-1964, treatment has been according to Tables III and IV of the standard Navy Recompression Tables,[2] promulgated in 1945. These tables involve recompression to six atmospheres pressure absolute, 165 feet depth equivalent, and slow stage decompression in ten foot increments over a 19 to 38 hour period, respectively. Treatment Tables III and IV are shown in Figure 1.

Figure 1. Standard Navy Recompression Tables for the Treatment of Air Embolism (from Table i-21, U. S. Navy Diving Manual).

If symptoms relieved within 30 min. after recompression to 165' use Table III	If symptoms NOT relieved within 30 min. after recompression to 165' use Table IV

Rate of Ascent between stops — one minute.

Feet	Table III	Table IV
165	30 min (air)	30 to 120 min (air)
140	12 min (air)	30 min (air)
120	12 min (air)	30 min (air)
100	12 min (air)	30 min (air)
80	12 min (air)	30 min (air)
60	30 min (0_2 or air)	6 hr (air)
50	30 min (0_2 or air)	6 hr (air)
40	30 min (0_2 or air)	6 hr (air)
30	12 hr (air)	11 hr (air), then 1 hr (0_2 or air)
20	2 hr (air)	1 hr (air), then 1 hr (0_2 or air)
10	2 hr (air)	1 hr (air), then 1 hr (0_2 or air)

In an effort to reduce the treatment time in the pressure chamber, the risk of decompression sickness occurring as a result of recompression treatment, and the rate of symptom recurrence and residual after treatment, a departure from the standard treatment of air embolism was undertaken in the cases occurring since 1964. The basis for this departure was derived from the work of Goodman and Workman at the Navy Experimental Diving Unit, Washington, D. C.[3]

This regimen consists of a rapid recompression and a high-pressure oxygenation phase. In the first phase, initial repressurization to 165 feet depth equivalent is made rapidly in order to relieve the major symptoms occurring from the acute embolization. This aspect of the treatment is unchanged from previous methods. Upon improvement in the patient's condition, the second phase is begun in which an ascent to 60 foot depth equivalent is made over a four minute period. At this point oxygen breathing, alternating with shorter periods of air breathing, is begun. After completion of the 0_2 — air sequence at the 60 feet stop, continuous decompression to the 30 feet stop is accomplished at a one foot per minute rate while the patient is breathing oxygen. At 30 feet alternate oxygen and air breathing is again carried out, followed by continuous decompression to the surface at the same rate as before again breathing oxygen.

The relative amount of time alloted to oxygen breathing and air breathing respectively in each of the sequences has varied during the evaluation of this approach to treatment. The change in schedules for this second phase have essentially followed the evolution of the oxygen breathing tables developed by Goodman and Workman for the treatment of decompression sickness and are shown in Figure 2.

Figure 2. Comparison of Oxygen Sequences Evaluated for the Second Phase of the RR-HPO Treatment of Air Embolism.

Depth (Feet)	Earlier Table V (1964-1965)	Later Table V (1966-1967)
	Symptoms relieved within fifteen minutes after recompression to 165 feet	
60	40 min. 0_2	one or two periods — 20 min. 0_2, 5 min. air
60-30	30 min. 0_2	unchanged
30	30 min. 0_2	one or two periods — 20 min. 0_2, 5 min. air
30-0	30 min. 0_2	unchanged
	Symptons NOT relieved within fifteen minutes after recompression to 165 feet	
60	30 min.0_2, 15 min. air, 30 min 0_2	three or four periods — 20 min. 0_2, 5 min. air
60-30	30 min. 0_2	unchanged
30	two periods — 15 min. air, 60 min. 0_2	unchanged
30-0	30 min. 0_2	unchanged

Initially, thirty to forty minutes of uninterrupted oxygen breathing was performed at the 60 foot stop. Later, in order to reduce the risk of oxygen toxicity, the time of uninterrupted oxygen breathing at 60 feet was limited to twenty minutes. In cases in which more than one twenty minute exposure was utilized, the oxygen breathing periods were separated by five minutes of air breathing as opposed to the earlier schedule in which a fifteen minute air breathing stop separated a sequence of thirty minute oxygen exposures.

Two treatment sequence aspects have remained unchanged. One is the use of sixty minute oxygen exposures separated by fifteen minute air exposures at 30 feet in those cases in which major symptom response at 165 feet took longer than ten minutes. The second is that the ascents from 60 feet to 30 feet and again from 30 feet to the surface has occurred over a thirty minute period during which time oxygen breathing is utilized.

The selection of the treatment table is determined by the amount of time required for major symptom relief at 165 feet. The shorter table, corresponding to that used for severe decompression sickness responding promptly to high pressure oxygenation treatment, is known as Table V. If more than fifteen minutes was required for major relief, then a longer oxygenation schedule is required. This sequence is now known as Table VI, and corresponds to the table used for the treatment of serious decompression sickness not responding after ten minutes of oxygenation at 60 feet. Tables Va and VIa now refer to the total treatment schedules for air embolism consisting of both the rapid recompression and the respective oxygen breathing phases. They are shown in Figure III along with instructions for their use.

Figure 3. RR-HPO Treatment of Air Embolism.

TABLE V-a — PATIENT SYMPTOM FREE WITHIN 15 MINUTES

Depth (Feet)	Time (Min.)	Breathing Media	Total Time (Min.)
165	15 or less	Air	15 (*)
165-60	4	Air	19
60	20	0_2	39
60	5	Air	44
60	20	0_2	64
60-30	30	0_2	94
30	5	Air	99
30	20	0_2	119
30	5	Air	124
30-0	30	0_2	154

TABLE VI-a — PATIENT SYMPTOM FREE WITHIN 30 MINUTES AND/OR RAPIDLY IMPROVING

Depth (Feet)	Time (Min.)	Breathing Media	Total Time (Min.)
165	30 or less	Air	30 (*)
165-60	4	Air	34
60	20	0_2	54
60	5	Air	59
60	20	0_2	79
60	5	Air	84
60	20	0_2	104
60	5	Air	109
60-30	30	0_2	139
30	15	Air	154
30	60	0_2	214
30	15	Air	229
30	60	0_2	289
30-0	30	0_2	319

(*) Total time will vary as function of this stop.

INSTRUCTIONS FOR USING TABLES

1. DESCENT TIME — Récompression to 165 feet should be accomplished as rapidly as possible (usually less than one minute).
2. TIME AT DEPTH — Total time at 165 feet will vary with the clinical status of the patient. The medical attendant should take the time to make a thorough physical appraisal of the patient, since the ensuing treatment is based on the patients physical status.
3. USE OF TABLE V-a — If all major symptoms and signs are gone before 15 minutes total bottom time, proceed to 60 feet at 25 feet per minute and begin oxygen breathing according to Table Va.
4. USE OF TABLE VI-a — If serious or major symptoms or signs persist beyond 15 minutes, but show signs of moderating within 30 minutes total bottom time, proceed to 60 feet at 25 feet per minute and begin oxygen breathing according to Table VI-a.
5. SERIOUS SYMPTOMS — Such include unconsciousness, convulsions, major paralysis or weakness, cranial nerves signs, and cerebellar signs.
6. PERSISTENT SYMPTOMS — Should serious symptoms and signs persist beyond 30 minutes **without moderation,** begin Table IV treatment.
7. ATTENDANTS — Inside tenders routinely breathe air; however, if treatment constitutes a repetitive dive for a tender, he must breath 0_2 from 30 feet to the surface.
8. OXYGEN TOXICITY — Should symptoms or signs of oxygen intolerance develop at the 60 foot stop, the oxygen should be discontinued temporarily and begun again on leaving the 60 foot stop.

9. FOLLOW-UP — On completion of the treatment table the patient should be routinely held for observation and given a thorough medical examination, including appropriate radiographic and laboratory studies. Patient should be released only if completely asymptomatic.

RESULTS OF TREATMENT

There have been a total of twenty-four over-pressurization accidents occurring at the New London tank from 1956 through June 1967, as a result of buoyant ascent and Steinke hood training. In addition, one case of air embolism developing as a result of free ascent was treated and is included. (In this latter technique the individual on ascent releases only enough air from his lungs, initially fully inflated with air pressurized to depth, to prevent embolization and yet maintain positive buoyance. The training in this particular method is considerably more dangerous and is not generally taught at the present time.)

Four of the cases exhibited the production of extra-alveolar air, such as pneumothorax or subcutaneous emphysema, but not cerebral air embolism. Recompression was not a part of their treatment, and these cases are not included in the treatment figures.

One of the twenty-four cases resulted in death. While this is certainly a treatment failure, it cannot be considered a failure of any particular regimen because of the short time, approximately four to five minutes, that the patient was under recompression prior to death.

Nineteen of the cases developed air embolism and were treated by recompression in one form or another. A summary of the methods of treatment is given in Figure 4.

Figure 4. Treatment of Surviving Cases of Air Embolism Occurring at the Escape Training Tank, New London, Connecticut, 1956-1967.

	Table III		Table IV		RR-HPO	Method	Other Methods	
	Used	Failed	Used	Failed	Used	Failed	Used	Failed
Bouyant Ascent	7	1	2	0	6	0	0	0
Steinke Hood	2	0	0	0	1	0	1 170 ft 20 min.	0
Free Ascent	1	0	0	0	0	0	0	0
Total	10	1	2	0	7	0	1	0

Eleven of the nineteen surviving cases in this report were treated a total of twelve times according to the standard recompression tables. There was one treatment failure on Table III, occurring while under pressure at 30 feet depth pressure equivalent. The case was ultimately treated with Table IV, with a resulting failure rate of 8.3%, in this series for the Standard Tables.

The Navy-wide experience with Tables III and IV for the treatment of air embolism is even poorer.[4] From 1946 through 1962, forty-six surviving cases of air embolism of all causes were treated by several Navy facilities, primarily the escape training tanks at the Naval Submarine Bases, Groton, Conn., and Pearl Harbor, Hawaii. This group includes the escape training accident cases discussed in this paper which occurred at the New London Tank during that time period. In the seventeen year interval, the rate of symptom recurrence and/or residual incidence following treatment was 19.5%, seven failures having come in the use of Table III in thirty-four cases and two failures occurring in the twelve cases treated according to Table IV.

This larger group of air embolism cases resulted not only from submarine escape training at the two training tanks but also from accidents occurring while diving in open water. In the latter situation the time between the occurrence of the accident and the application of treatment recompression is often greater than that following escape training accidents because of the distance of the patient from the recompression chamber at the time of the accident. This may be one of the factors accounting for the higher residual and recurrence rate.

During the 17 year period under review, five persons died as a result of air embolism.

Though they may be classed as treatment failures, none is included in the group, since all died before or shortly after recompression had been instituted. It may be noted that four of the deaths occurred following free ascents. The fifth fatality is the one mentioned earlier in the paper.

A summary of the cases occurring since 1964, and treated by the newer, shorter approach is given in Figure 5. All seven of the cases in which RR-HPO method was used have been successfully treated without symptom recurrence or permanent residual. None of the patients developed decompression sickness as a treatment sequalae. The average treatment time was approximately three hours. In all but one of the cases, relief of major symptoms was obtained within fifteen minutes after the initiation of rapid recompression, and so their treatment schedule more nearly approximated Table V-a. In the remaining case, Table VI-a was followed because of incomplete resolution of paresthesia and paresis.

There was one case which was treated with rapid recompression and then decompression according to a standard Navy 170 feet for 20 minute table with no Hyererbark Oxygen Breathing. The patient had already responded completely before reaching 100 feet on recompression. After spending two minutes at 165 feet he was successfully decompressed in twenty-five minutes, utilizing a recompression ascent rate of 25 feet per minute. Six minutes were required for ascent to the first stop at 20 feet where four minutes were spent, followed by fifteen minutes at 10 feet.

Figure 5. Summary of Eight Cases of Air Embolism Associated with Escape Training at Groton, Connecticut, Oct 1964—Mar 1967.

CASE	DATE	DIVE	TREATMENT	OUTCOME & ADDT'L DIAGNOSIS
1. M.H.M.	10-15-64	B.A.	165′ + early Table 5	Return to duty in 48 hrs.
2. C.C.N.	3-12-65	S.H.	165′ + early Table 5 — modified — *	Return to duty in 24 hrs.
3. B.S.T.	1-14-66	S.H.	165′ + Table 170/20 — no O_2 — *	Return to duty in 24 hrs.
4. J.H.D.	5-26-66	B.A.	165′ + later Table 5	Return to duty in 24 hrs.
5. J.H.	6-15-66	B.A.	165′ + later Table 5*	Return to duty in 24 hrs.
6. F.J.B.	9-23-66	B.A.	165′ + later Table 5	Mediastinal Emphysema* Return to duty in 5½ days
7. D.D.M.	10-24-66	B.A.	165′ + later Table 5	Residual Chest Pain* Return to duty in 2½ days
8. B.R.M.	3-8-67	B.A.	165′ + later Table 6*	Return to duty in 3 days

*SPECIAL NOTES:

Case 2—60 feet stop was bypassed. O_2 breathing at 30 feet stop and 30-0 feet. Attendant developed mild decompression sickness.

Case 3—Standard Navy Decompression Table used.

Case 5—Developed signs of early O_2 intolerance after 15 min. at 60 feet—changed to air breathing—returned to O_2 on leaving the 60 feet stop.

Case 6—Subsequent chest X-ray showed pneumopericardium.

Case 7—Subsequent EKG showed inverted T waves which reverted to normal in 2 days.

Case 8—Because of a question of persistence of paresis and paresthesias at 165 feet, Table 6A was used.

B.A.—Buoyant Ascent

S.H.—Steinke Hood

DISCUSSION

The rationale for the use of the high pressure oxygen breathing phase after initial sympton relief is two-fold. One is the desire to reduce the length of time at such depths as is required in treatment according to Table III or IV. With each increase in time and depth under pressure there is a greater uptake of inert gas by the tissues. This not only increases the possibility of the subsequent development of treatment related decompression sickness, either following or during treatment, but also diminishes the rate of diffusion from the tissues of gas that has been absorbed in the same pressure exposure that led to the embolization accident. With the use of oxygen, the uptake of inert gas by surrounding tissues is completely eliminated, thereby creating a maximal gas exchange gradient from the tissue to the surrounding fluids. The second reason is the increased tissue oxygenation aiding in "functional restoration of tissues rendered hypoxic by the ischemic action of bubble emboli."[3]

The minimal depth, oxygen breathing tables were tested both clinically and hypothetically and found to provide adequate decompression for pressure exposures which initially had received grossly inadequate decompression. If the tables are not properly followed, however, decompression sickness may result. Such did occur with a chamber attendant caring for patient 2 (C.C.N.). In bypassing the 60 foot stop, inadequate decompression resulted and the attendant who did not breathe oxygen during the treatment sequence, developed mild decompression sickness, manifested by skin rash and joint pains of the upper extremities.

The importance of rapid recompression is obvious in all cases treated, as generally symptoms are relieved within minutes after recompression. Its contribution to the total treatment regimen can be seen especially in two cases. In case 3 (B.S.T.), treatment consisted only of rapid repressurization, there being no oxygenation phase at all. The oxygenation phase in case 2 (C.C.N.) was markedly reduced. The patient was decompressed from 165 to 30 feet before beginning an oxygen stop. This second treatment, however, did create the setting for decompression inadequacy mentioned above.

The rapidity with which cerebral vascular function is restored by repressurization following the occurrence of experimentally produced cerebral air embolism has been graphically demonstrated by Waite, et al.[5] Dogs were prepared by making a window in the calvarium and exposing cerebral vessels. Air was injected into an isolated carotid artery and the subsequent appearance of bubbles and vascular occlusion was observed in the exposed cerebral circulation. The group of animals which were treated were then pressurized to 165 feet pressure equivalent. Maximal restoration of circulation was seen at between 33 feet, two atmospheres pressure absolute, with evidence of a change in bubble size and partial restoration just beyond 33 feet and removal of all bubbles by 100 feet. These depths were achieved in a matter of seconds to a few minutes after the initiation of pressure. Decompression was accomplished with Navy tables using a 170 feet for ten minute schedule, using a 25 feet per minute rate of ascent and a two minute decompression stop at ten feet.

Five of the six embolized animals treated in this manner responded completely, indication that it is not the prolonged decompression in a schedule such as Table III or IV that is the beneficial factor in treating air embolism. Rather it is the promptness of the application of pressure that determines the speed of restoration of cerebral circulation. The one case not responding properly to treatment was the one in which rupture of a blood vessel with subsequent cerebral hemorrhage and edema occurred after embolization. This sequence of events may well give insight into the mechanism of the situation in which embolization is not promptly relieved by repressurization.

The fact that the RR-HPO treatment regimen is not only effective but also shorter in length than the standard Navy treatment schedule makes it even more beneficial. The patient and tenders are not subjected to the confining and uncomfortable environment of a recompression chamber for prolonged periods of time. Also the reduction of the length of the chamber stay permits the utilization of the full supportative facilities of the hospital sooner.

SUMMARY

Discussion of the treatment of traumatic cerebral air embolism by both standard Navy Recompression Tables and the new rapid recompression, high pressure oxygen breathing approach is presented. Seven cases occurring as a result of submarine escape training at the Escape Training Tank, Naval Submarine Base New London, Groton, Connecticut, and successfully treated with the latter method are presented. Factors regarding the rationale of the use of this new approach are given. POSTSCRIPT: Since the writing of this paper, the Navy Department has approved the treatment schedules recommended herein for the treatment of traumatic air embolism.

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CEREBRAL AIR EMBOLISM I. BASIC STUDIES

by

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SUBMARINE MEDICAL RESEARCH LABORATORY
U. S. NAVAL SUBMARINE MEDICAL CENTER REPORT NO. 493

Bureau of Medicine and Surgery, Navy Department
Research Work Unit MR005.04-0055.09

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SUMMARY PAGE

THE PROBLEM

To create an experimental model to study cerebral air embolism in live animals and to determine the role of compression and varying decompression on the outcome.

FINDINGS

A successful method of artificially producing and observing cerebral air embolism in live dogs was developed. The use of pressure to effectively treat this condition was reaffirmed and indications were found that prolonged decompression following compression to 165 feet is not necessary.

APPLICATIONS

Direct application of the experience and data collected is found in a possible modification to the current treatment of human cerebral air embolism as incurred by submarine personnel in escape training, SCUBA divers and aerospace personnel subjected to explosive decompression.

ADMINISTRATIVE INFORMATION

This investigation was conducted as a part of Bureau of Medicine and Surgery Work Unit MR005.04-0055—Pathological Physiology of Air Embolism and Decompression Sickness. The present report was approved for publication on 18 April 1967 and has been designated as Submarine Medical Center, Submarine Medical Research Laboratory Report No. 493,—this is Report No. 9 on the Work Unit listed above.

PUBLISHED BY THE NAVAL SUBMARINE MEDICAL CENTER

ABSTRACT

Using surgically created cranial windows and artificially producing cerebral air embolism by injecting air into the carotid arteries of live dogs, it was possible to observe the behavior and ultimate effect of cerebral intravascular air on a series of animals under varying modes of treatment and an untreated control group.

The results in the untreated controls were uniformly poor, whereas animals with cerebral air embolism who were treated with prompt recompression to 165 feet responded uniformly well. Only normal diving decompression was given and prolonged decompression, as in Navy treatment Tables III and IV, was not utilized. These results would indicate that the principle mode of therapy in air embolism should be rapid compression and **not** prolonged decompression.

CEREBRAL AIR EMBOLISM

I. BASIC STUDIES

INTRODUCTION

Traumatic cerebral air embolism is an acute, serious, occupational hazard associated with decompression and incurred by submarine personnel undergoing escape training, by individuals pursuing SCUBA diving as a vocation or hobby, and by aerospace pilots exposed to explosive decompression at ambient pressures of less than one atmosphere (1, 2, 3, 4). This condition should not be confused with decompression sickness (bends) which, though also related to decompression, has a somewhat different etiology and pathophysiology. In general, bends is less acute and tends in the average case to be of less serious import.

The designation 'traumatic' is proposed to differentiate this form of air embolism incurred in a diminishing ambient pressure from the 'accidental' variety occurring at one atmosphere in a hospital setting (5, 6, 7, 8, 9, 10).

The relationship of morbidity and mortality to the mode of escape training which has changed through the years is given in Figure 1, and can be seen to influence both traumatic and accidental types of embolism. Free ascent training is technically more difficult to master and has a resulting higher rate of occurrence of embolism than was found in older escape methods. The mastery of this technique by SCUBA divers is a necessity, if air embolism is to be avoided.

The incidence of dysbaric cerebral air embolism in relationship to submarine escape training at the Submarine Base New London, (Groton, Connecticut), in the past 35 years is given in Table I.

The National Safety Council estimated 60 deaths in 1965 were caused by SCUBA diving accidents, and a number of these were undoubtedly due to air embolism.

In the illness which is the subject of this series of experiments, the individual diver or submariner, is in a diminishing pressure situation which causes an expansion of gas in the pulmonary alveoli. If the normal exhalation route of the expanding alveolar gas is interrupted either voluntarily, as in breath-holding, or involuntarily, from trapped air, associated with pulmonary tract pathology, then the over-expansion and rupture of alveoli ensues. The gas is released into the pulmonary circulation and enters the cerebral circulation via the pulmonary vein, left heart, aorta and carotids. See Figure 2.

The pulmonary events, including the vital relationships of transpulmonary and transatrial pressures leading to alveolar rupture, have been well defined, (11, 12, 13, 14, 15, 16).

The wide clinical spectrum of symptoms and signs associated with cerebral air embolism include: Headache; vertigo; cranial nerve involvement; visual, auditory, and speech disturbances; loss of vital signs; and death.

Similarly, the coincident intrathoracic complications of pulmonary interstitial emphysema, mediastinal emphysema, and pneumothorax, have been studied and reviewed in several excellent papers, (12, 13). The cerebral events, however, have not been studied as closely, except in reports defining the clinical symptoms and signs and reviewing the experience with pressure therapy, (4, 17, 18, 19, 20).

Neither has the pressure treatment of cerebral air embolism been thoroughly evaluated or given the attention it deserves as the treatment of choice. Currently, there is little evidence, other than clinical, that speaks to the efficacy of six atmospheres

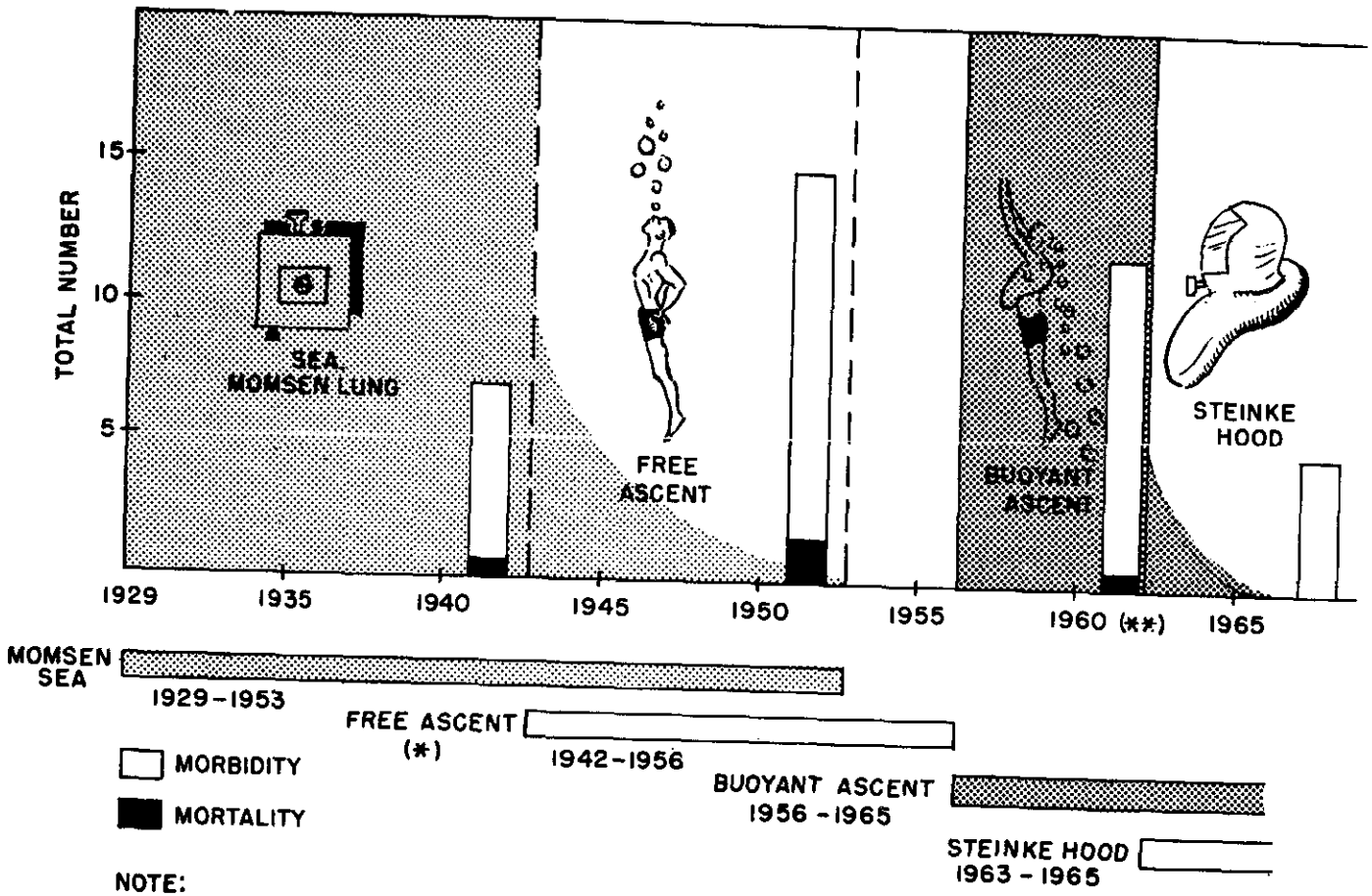

Figure 1. — Chronological Chart of Modes of Submarine Escape Training in the U. S. Navy.

YEARS	MODE	TOTAL NO. ESCAPES	TOTAL NO. AIR EMBOLISM (MORBIDITY)	DEATHS MORTALITY
1930-1953	S.E.A. MOMSEN LUNG	193,000	7	1
1942-1957	FREE ASCENT	17,583	15	2
1957-1965	BUOYANT ASCENT	130,679	12	1
1963-1965	STEINKE HOOD	32,679	5	0

Table I. — Morbidity and Mortality in Relation to Total Number of Simulated Escapes and Modes of Escape, U. S. Naval Submarine Escape Training Tank, New London, 1938-1963

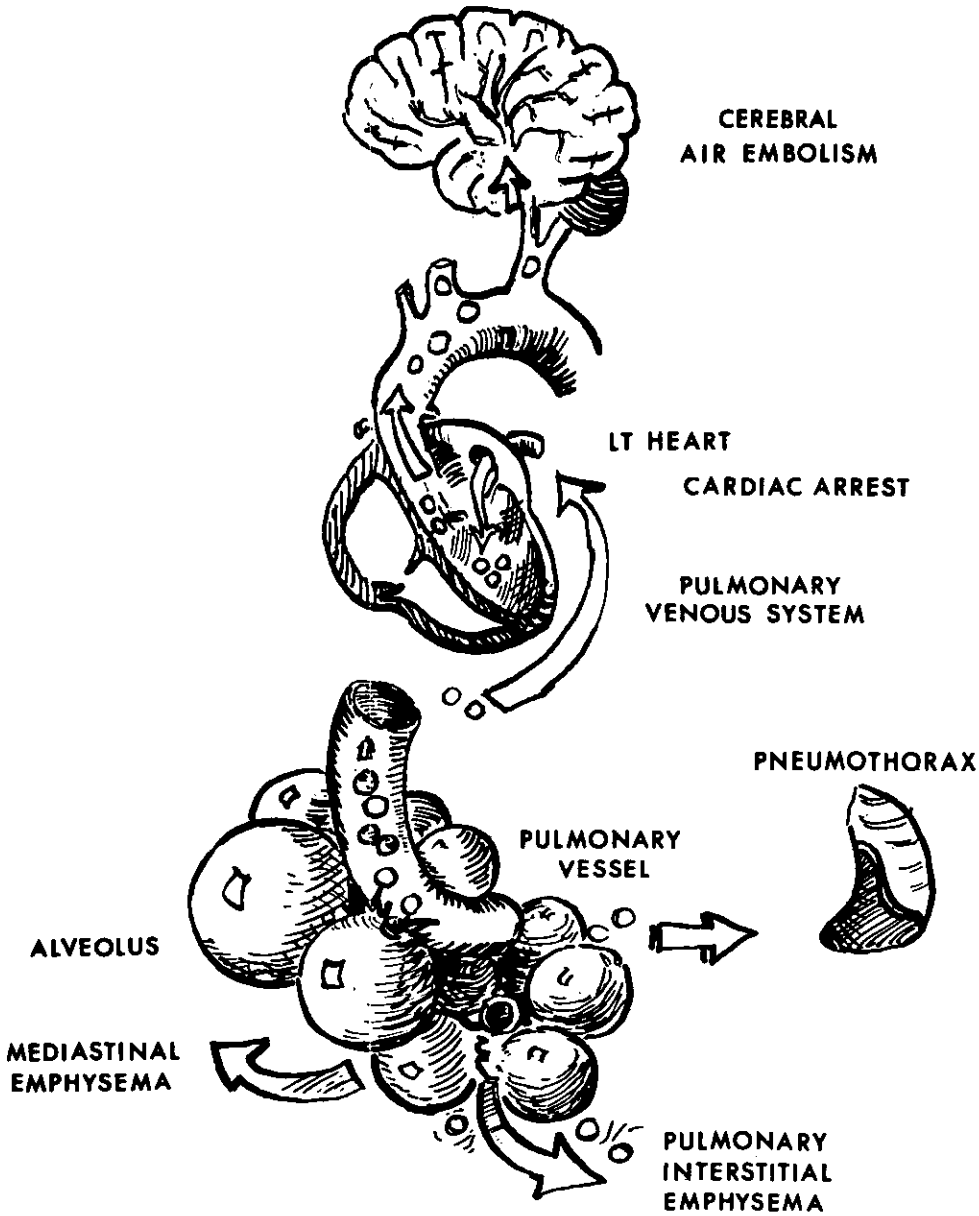

Figure 2. — Schematic of Potential Courses of Air from Ruptured Alveoli.

absolute of pressure as the optimum recompression required. At the same time, there is meager published evidence that pressures less than six atmospheres absolute are totally efficacious, (1, 2, 22).

Current thinking in the treatment of pressure illnesses tends towards less prolonged exposure of damaged tissues to high partial pressures of inert gas (24). This principle may also be applicable to the treatment of air embolism.

The occasional so-called "recurrence" of cerebral air embolism during the pressure treatment phase is a doubtful circumstance, more likely due to post-embolic cerebral damage, edema, and increased intracranial pressure.

The series of experiments to be described is directed toward a better understanding of the cerebral events of air embolism and the effects of recompression in the natural history of the injury, —all with a view toward developing a more effective treatment.

PURPOSE OF THE STUDY

The purposes of this study are listed below:

(1) To develop a technique to produce and observe cerebral air embolism in vivo in mammals with a high degree of consistency;

(2) To observe grossly the effect of cerebral intravascular bubbles on the cerebral circulation and the tissues supplied by the cerebral circulation;

(3) To observe in vivo the life history of cerebral intravascular air and its residual effect on the untreated embolized animal;

(4) To observe in vivo the life history of cerebral intravascular air and its effect on cerebral tissue using immediate recompression to 165 feet (six atmospheres absolute) as the mode of treatment.

(5) To observe in vivo the cerebral cortex and cerebral blood vessels of embolized animals during the decompression phase, utilizing standard 170-foot/10 minute diving table. This is in lieu of the U. S. Navy Standard Treatment Tables III and IV. In this phase, particular attention will be paid to possible reappearance or recurrence of the cerebral intravascular air.

MATERIALS AND METHODS

Initial cerebral studies in vivo were done on prepared cats and small dogs, injecting air into the carotid and observing cerebral intravascular bubbles in the region of the frontal cortex. From these studies it was determined that dogs weighing 25-40 pounds were the most satisfactory species for these experiments.

Additionally, a cranial window technique was adopted to visualize the cortex. This was done using a modification of Pudenz and Shelden's lucite calvarium technique, (21). All subsequent animals used were mongrel dogs which were prepared with a unilateral cranial window 2.5 cm in diameter in the parieto-occipital area, except one dog which was prepared with bilateral cranial windows. These windows were created seven days prior to any experimentation in order to allow the animal to stabilize after the procedure. After four experimental runs with the cranial window, the visualization technique was changed to a simple craniotomy for all succeeding runs. See Figure 3.

Twenty-four hours prior to an experiment, the carotid artery on the same side as the window was dissected free and isolated through a cervical incision and sterile tape was looped around it. The tape was allowed to protrude through a partially closed incision and gave ready access to the carotid when embolization was desired.

Ambient air in the amount of 1-7 cc was injected into the carotid with an ordinary disposable syringe and 18 gauge needle to artificially produce the cerebral air embolism.

Figure 3. — Cranial Window (X3.3) as seen Through the Dissecting Microscope,—Note Air Filled Arteries as Indicated by Arrows.

Recording of Results:

Four modes were utilized to record the experiments. They were:

(1) Direct observation and tape recording;

(2) Six-frame-per-second photography, —color, and black and white.

(3) Color motion-pictures, —sound and silent;

(4) Closed circuit TV.

Types of Experimental Runs:

The types of runs with the embolized animals were varied to meet the objectives of the study. Initial experimental runs were concerned only with the production of a satisfactory cerebral air embolism, permitting observation of intravascular bubbles and their effect on the circulatory dynamics and the cerebral tissue supplied. In this series, five dogs in six separate runs were observed. All runs were done on the surface at 14. 7 p.s.i. (one atmosphere).

In the second series, three dogs were embolized at one atmosphere and taken to treatment depth, then returned to surface on a standard 170-foot diving decompression table for the appropriate time on the bottom. These are hereafter referred to as "bounce dives."

In another series, three dogs were embolized at 33 feet (two atmospheres), brought to the surface and then given bounce dive treatment to 165 feet. This was done to simulate the occurrence of cerebral air embolism in a decreasing ambient pressure environment, much as it occurs in the true situation. When dogs were embolized without treatment, the experiments were conducted in the veterinary operating suite. When the dogs were embolized and treated with pressure, the entire procedure was conducted in the large recompression chamber at the Submarine Medical Research Laboratory. This permitted room for observers, motion-picture cameras, TV monitors and monitoring equipment. See Figure 4.

RESULTS AND OBSERVATIONS

A total of 14 embolism experiments were conducted (see Table II). Three were unsuccessful, in that attempts to induce artificial cerebral air embolism via the carotid route could not be accomplished. This was invariably due to thrombosis of carotid vessel incurred during the preparation.

Five dogs were embolized and not given treatment with recompression; two expired within twenty minutes, and three survived, but with severe residual damage evident. The residual damage was evidenced by alterations in the state of consciousness, major paralysis, ataxia, incoordination, convulsions, muscle spasm, reflex changes, anorexia, and cranial nerve damage.

Of the six successfully embolized at one and two atmospheres, and then treated with recompression to 165 feet, five survived without demonstrable residual damage. One dog (#12) survived, but with severe residuals in evidence, of the type already described. On examination of the film record, (which took several weeks to process), a rupture of a cerebral vasculature was noted. Not only were the air bubbles expelled as a froth over the brain surface, but with restoration of the circulation by recompression, gross cerebral hemorrhage ensued. At autopsy, gross section of this animal's brain (see Figure 5) revealed a massive deep hemorrhage in the region of the area observed and reaffirmed by the motion-picture record.

Observations Concerning the Cerebral Intravascular Air:

With the cerebral window exposures performed, the observations for the most part were made on the anterior cerebellar and posterior cerebral branches of the posterior communicating artery of the carotid. The arterial vessels under observation with the dissecting microscope and motion-picture camera had diameters of from 30 microns to 2 mm.

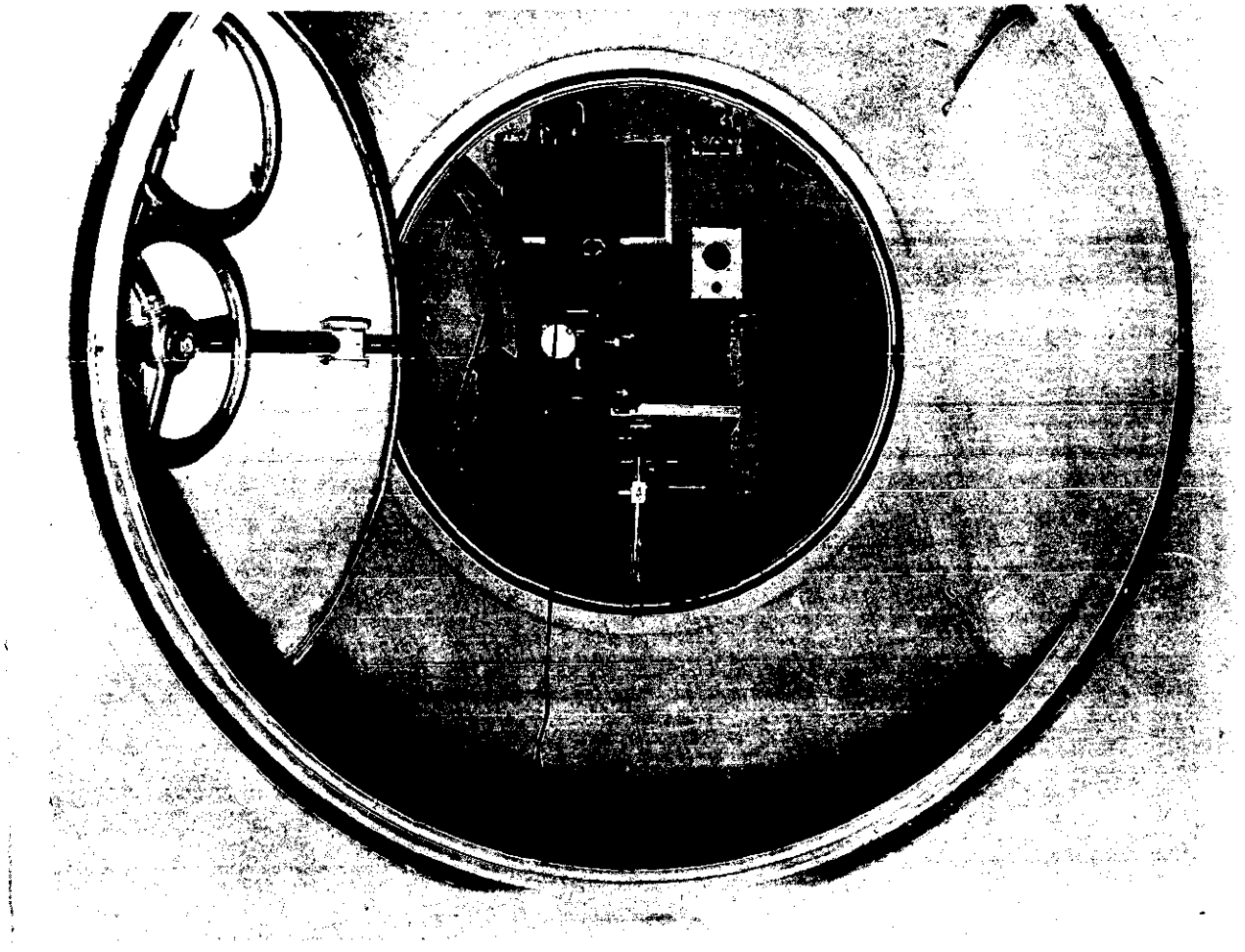

Figure 4. — Interior of Large Pressure Chamber Showing Experimental and Photographic Set-Up for Embolism Studies.

TABLE #2 SUMMARY OF OBSERVATIONS

Date	Animal	Type of Run	Amt. of Air Inj. Carotid	Cerebral intravascular bubbles observed	Treatment	Outcome & Remarks
10-23-64	Dog #1	Frontal lobe observation 1 atmosph.	5 cc	Yes	None	Circul. blocked - death in 18 min.
12-7-64	Dog #2	Temporal - cranial window - embolized at 1 atmosphere	2 cc	Yes	165 ft. bounce dive 170 ft. dive table	Cerebral intravascular bubbles disappeared 80-100' - dog survived
12-10-64	Dog #2	Temporal - cranial window - embolized at 33 ft.(2 atmosph.)	1 cc	Yes	None	Dog expired - 12 min. Circul.effect.blocked
1-15-65	Dog #3	Occipito-Parietal window 1 atmosphere	Repeated attempts to embolize unsuccessful	No	None	Unsuccessful Thrombosed Carotid
1-21-65	Dog #3	Occipito-Parietal window Embolized at 33 ft. (2 atmosph.)	1 cc	Yes	Surfaced - then 165 ft.bounce dive 170 ft.dive table	Very poor on surface - survived - no residuals bubbles gone at 100 ft.
1-30-65	Dog #4	Bilateral Occipito-Parietal windows	Repeated attempts to inject air unsuccessful	No	None	Unsuccessful Thrombosed vessels - Dog survived
2-5-65	Dog #5	Bilateral Occipito-Parietal Embolized at 1 atmosph.	5 cc	Yes	165 ft.bounce 170 ft.dive table	Cerebral intravascular bubbles gone at 100 ft.
5-27-65	Dog #6	Lt. craniotomy Embolized at 1 atmosph.	5 cc	Yes	None	Proved bilateral widespread distribution of air from unilateral carotid injection - dog sacrificed
6-15-65	Dog #7	Lt. craniotomy Embolized at 1 atmosphere	5 cc	Yes	165 ft. bounce dive 170 ft. dive table	TV camera run successful - dog survived Bubbles no longer observed after 60 ft.
12-15-65	Dog #8	Lt. craniotomy Embolized at 1 atmosphere	Repeated attempts to embolize unsuccessful	No	None	Unsuccessful run - thrombosed vessels
12-15-65	Dog #9	Lt. craniotomy Embolized at 1 atmosphere	7 cc	Yes	None	Dog survived with serious residuals - sacrificed at 20 days - post-embolism Autopsy
1-17-66	Dog #10	Lt. craniotomy Embolized at 1 atmosphere	7 cc	Yes	165 ft. bounce dive	Dog survived - no residuals
1-17-66	Dog #11	Skull intact	5 cc	No	None	Survived with residuals
1-18-66	Dog #12	Lt. craniotomy 2 atmospheres	7 cc at 33 ft.	Yes	165 ft. bounce dive	Survived but with severe residuals - dog sacrificed Film record shows severe cerebral hemorrhage coincident with bubble insult. No intravascular bubbles after 80 ft. Autopsy

Table II. — Results of Fourteen Animal Embolism Experiments.

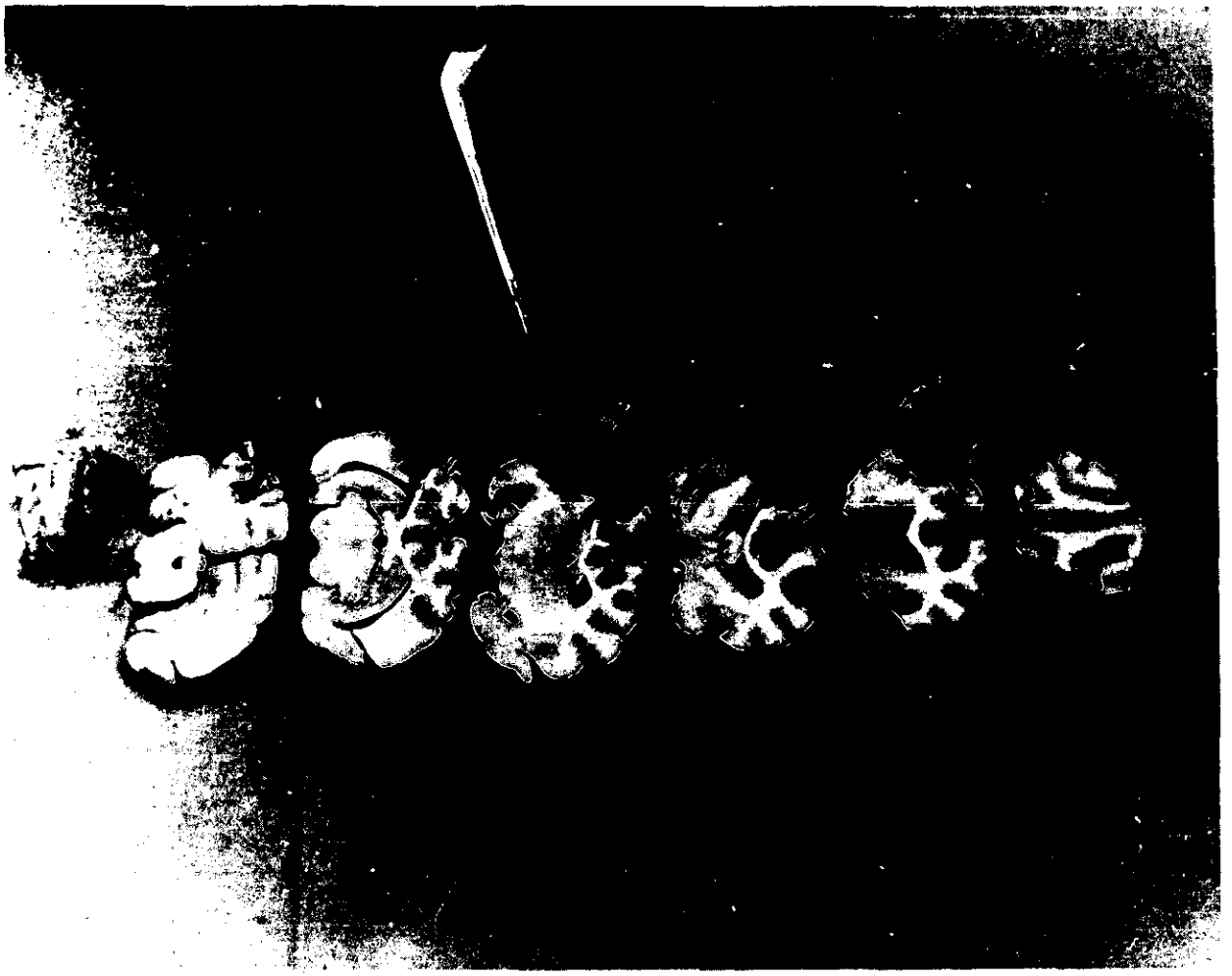

Figure 5. — Cerebral Sections Showing Gross Hemorrhage Which Occurred Coincident With Run No. 14 (Dog No. 12).

Typically, the bubbles conformed to the size and shape of the blood vessels. The majority of the air passed through the larger arteries very rapidly, but on reaching the branches of these arteries came to rest in a way that effectively blocked arterial circulation. In some instances, entire branches were filled with air; in others, the air bubbles were lined up in a row with small amounts of blood separating them with thin biconcave menisci. The very small arteriolar vessels were completely filled with air and appeared as a very thin, silvery network on the cortical surface. The largest arteries observed to be blocked by the bubbles were 2 mm in diameter. However, most of the vessels observed which were filled with air and showed evidence of circulatory obstruction were smaller than 2 mm, and were in the range of 30-60 microns. This confirmed the observations of Curtillet and Curtillet (23), who, doing similar work on dogs in 1939-40, reported effective blockage in arterioles of 30-40 microns in diameter.

At the blood/air interfaces, the circulation was at a standstill, and the pulsations of the heart could be seen. In other small arteries there was a slow pulsating progression of the bubbles in response to the systolic pressure peaks. In the series of photographs (Figure 6) a progression of such a bubble can be seen. The pulsating nature of the progression can be seen by the small amount of blood pushed into a branch and then left behind by the recession of the pulse (Figure 6-C).

The surrounding brain tissue exposed by the cranial windows came under observation and typically showed a pallor which in the untreated cases gave way to a reactive hyperemia. Minor flare hemorrhages and petechial air embolism were also noted. Moderate edema was evident in some cases after an hour or more.

In the six dogs embolized and then recompressed to 165 feet, the following results were observed: Two showed that all the bubbles observed grossly had vanished by 100 feet (four atmospheres); three showed the same results by 80 feet; and one dog, by 60 feet.

In every instance there was evidence of a change in bubble size and partial restoration of the circulation just beyond 33 feet. In none of the experiments were intravascular bubbles seen to persist after pressure equivalent to four atmospheres was reached.

Equally important, in no instance was there a reappearance of bubbles during or after decompression, using a Standard Navy Decompression Table for 170 feet (10 min.) at a standard ascent rate of 25 feet per minute.

There was no attempt in this series to treat cerebral air embolism with pressures less than six atmospheres absolute, even though there is some indication that this maximum need not be applied.

A future series is planned, using four atmospheres and the no-recompression control series.

COMMENTS AND CONCLUSIONS

In the past, the civilian medical community has not given the pressure therapy of cerebral air embolism the recognition it deserves as the treatment of choice. This was undoubtedly due to the general nonavailability of such facilities in the average hospital setting. Today, however, the current interest in hyperbaric medicine has resulted in the establishment and maintenance of pressure facilities in many leading medical centers throughout the country. Personnel responsible for these facilities should develop an awareness, and indeed the technical competence, to treat decompression sickness and air embolism. With this capability, the facility can be used to treat not only the occasional air embolism seen in clinical medicine, but the increasing number of civilian SCUBA diving accidents as well.

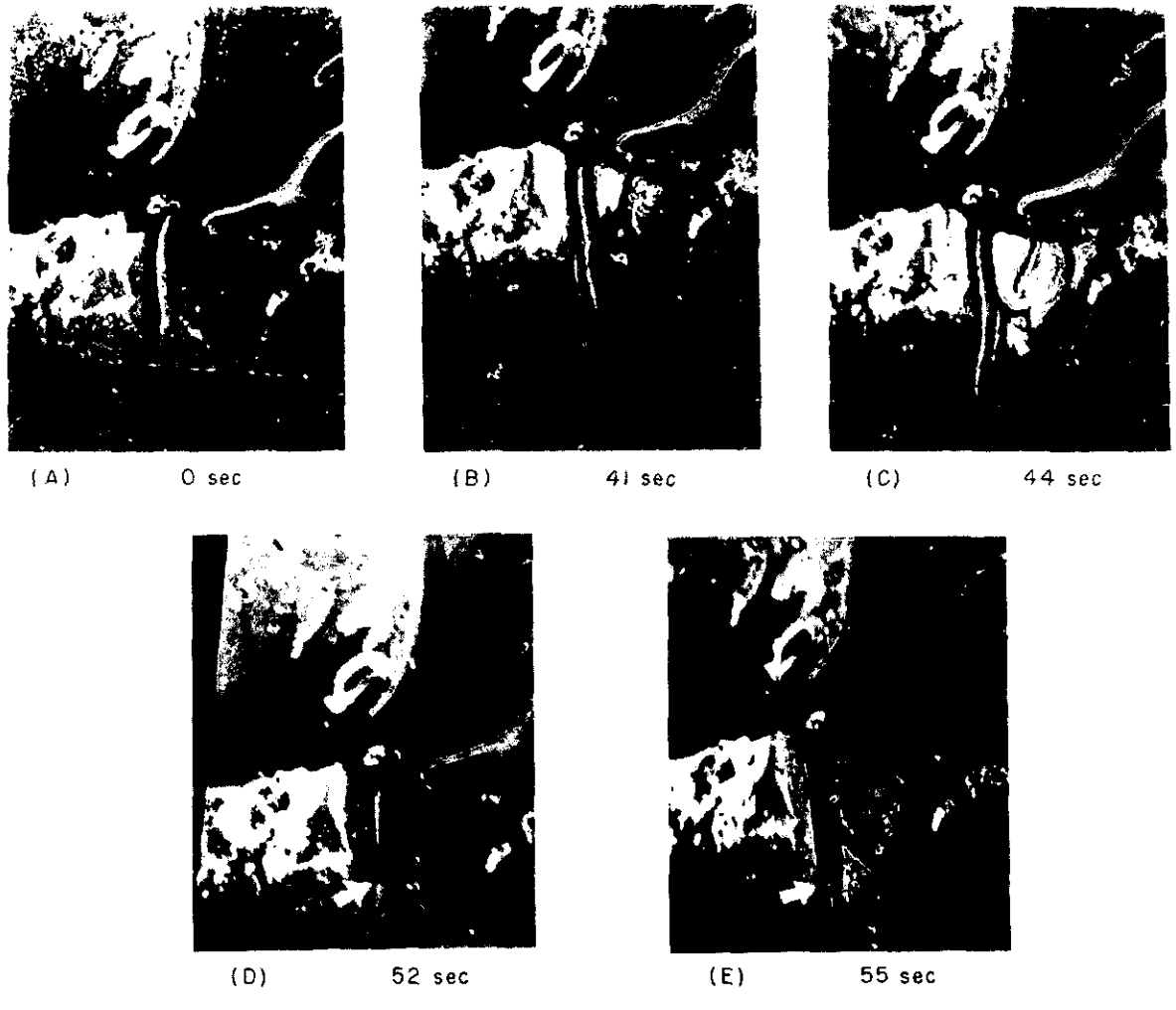

Figure 6. — Cerebral Artery (1 mm. in diameter), Showing Progress of Circulation Against Untreated Air Embolism (6 fr/sec). Indication of pulsation can be seen in 6C.

The present study, while limited in scope and design, did accomplish the following:

(1) A technique for observing and photographing intravascular cerebral air embolism in vivo was developed and refined;

(2) In a controlled series, the efficacy of pressure as a means of relieving the circulatory obstruction caused by air embolism was observed and reaffirmed;

(3) There were indications of the pressures necessary to relieve the air embolism. Maximum effects of recompression were observed between 33 feet (two atmospheres absolute) and 100 feet (four atmospheres absolute). Until further experiments are performed, however, there is sufficient evidence to permit one to say that the maximum pressure of 165 feet (six atmospheres absolute) should be considered as unnecessary;

(4) Additionally, there was good indication that prolonged recompression, as in Tables III and IV of the U. S. Navy Standard Treatment Tables, is not necessary to effectively treat cerebral air embolism. All of the successful pressure treatment runs in this series consisted of bounce dives to 165 feet for less than ten minutes and return to the surface at 25 feet per minute with a two-minute stop at ten feet (170 ft. Table);

(5) The role of post-embolic edema could not be measured or evaluated because of the unrealistic presence of the cranial window which undoubtedly modified this reaction;

(6) Ideas for additional studies were developed.

In future studies in this series, it is planned to:

(1) Evaluate the effect of treatment using pressures less than six atmospheres absolute;

(2) Evaluate the effects of hyperbaric oxygen at 60 and 30 feet, added to the pressure treatment regimen.

SUMMARY

The medical aspects and pathophysiology of cranial air embolism are briefly reviewed. The term "dysbaric cerebral air embolism" is proposed to differentiate this condition, incurred in a diminishing ambient pressure, from the "accidental" type seen in the hospital setting at the constant pressure of one atmosphere.

A method of artificially inducing cerebral air embolism and observing and photographing the intravascular cerebral air in living dogs is described.

Observations on the life history and behavior of cerebral arterial air at one atmosphere absolute (14.7 p.s.i.) and the effect of pressure therapy to six atmospheres absolute (88 p.s.i.) and subsequent decompression to one atmosphere are presented.

The use of pressure in effectively treating cerebral air embolism is reaffirmed, and there is indication that a prolonged decompression following recompression to 165 feet is not necessary.

The present study confirms that six atmospheres absolute is effective in grossly relieving cerebral air embolism. Effective treatment with pressures less than six atmospheres awaits further study.

Additional studies are proposed.

NOTE: A film, entitled "Cerebral Air Embolism" (12-min. color-sound) was made at the Naval Submarine Center, which shows some of the experiments conducted and described in this paper.

The cranial window and carotid artery preparation of the dogs are shown. Two typical air embolism experiments are depicted with closeups of the embolism and its effect on cerebral vasculature and tissue in living dogs. The first is an untreated case at one atmosphere, and the second a treated case using pressure to 165 feet. The effect of pressure in relieving the air embolism is seen. The clinical neurological effects after embolization are shown and compared for both cases.

A special case is shown in which the rupture of a cerebral vessel is seen to occur coincident to the insult of air embolism. (Film is unnumbered; but three copies are available on loan from Commanding Officer, Submarine Medical Center, Box 600 —Naval Submarine Base, Groton, Connecticut 06340).

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HYDROGEN-OXYGEN DIVING

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10

HYDROGEN-OXYGEN DIVING

P. O. EDEL

Although virtually all the literature dealing with use of hydrogen-oxygen as a breathing mixture is of recent origin, the first recorded experiment was reported almost 200 years ago. In 1789, the French chemist, Antoine Laurent Lavoisier (Seguin & Lavoisier, 1789) exposed guinea pigs to a hydrogen-oxygen atmosphere at sea level pressure in glass bells. He noted that the animals showed no discomfort for 8 or 10 h exposure, laying the groundwork for further experiments with this mixture. Thus, the report appears to be the obvious choice for the initial paper in this series.

Despite the evidence that hydrogen was not toxic (at least for acute exposures at 1 atm) no further work was done on the mixture for about 150 years. In 1941, the Russian scientist Lazarev (1943) succeeded in exposing animals to a hydrogen-air mixture under pressure. In the same year, the British scientists Case and Haldane (1941) reported an experiment in which they breathed a mixture of hydrogen-nitrogen-oxygen for 5 min at 10 atm in a dry chamber. These two papers were selected because they were the first to describe experiments with animals and man under pressure with hydrogen-oxygen breathing mixtures. More importantly, the successful conclusion of these experiments was undoubtedly influential in encouraging further work with this gas.

The next development was not long in coming. A few years later, the young Swedish engineer Arne Zetterstrom (1948) launched a program, with the assistance of the Royal Swedish Navy, encompassing a wide range of scientific and operational goals. In addition to design of shipboard systems for producing the gas mixtures and the design or modification of diving gear and handling systems for use with hydrogen-oxygen and hydrogen-nitrogen-oxygen mixtures, he made the first open water dives with this gas. He reported his successful dives to 110 m in a paper published shortly before his death in 1945. A later paper by Bjurstedt and Severin (1948) reports the decompression procedures in detail and describes Zetterstrom's final dive in which he attained a depth of 160 m, where he reported the absence of any symptom of narcosis. Due to a regrettable incident having no connection with the breathing mixture used, his diving stage was then brought directly to the surface, without any decompression stops, following his 20 min exposure at 160 m. The decompression sickness resulting from the omission of approximately 2 h of decompression resulted in the death of this valiant investigator. These two papers were chosen because, despite the death of Zetterstrom, his pioneering efforts were probably more influential than any other study in inspiring further research with hydrogen-oxygen mixtures, in addition to being the only investigation to date involving open water diving experience.

Later, Brauer and his colleagues (1967) included hydrogen-oxygen in their studies of the hyperexcitability phenomena in America. In 1967, they reported a series of experiments in which rhesus monkeys and female mice of the CB strain were compressed on various schedules to the convulsion thresholds on helium-oxygen and hydrogen-oxygen mixtures. A significantly higher convulsion pressure threshold was observed for hydrogen-oxygen, compared with helium-oxygen. In a parallel experiment with nitrogen-oxygen, narcosis was used as the endpoint, with no symptoms of fasciculation or convulsions at the pressures at which the tests were terminated. This led the authors to conclude that hydrogen was intermediate between the other two gases used in the study and that the relative narcotic potencies of nitrogen, hydrogen, and helium were 1:0.4:0.2.

In 1974, Brauer et al. used hydrogen, nitrogen, and nitrogen-oxygen as additives to helium-oxygen in a subsequent series with mice to successfully raise the pressure threshold of both the tremor and convulsion phases of HPNS. They concluded that the relative anti-HPNS potencies of these gases were related to their relative anesthetic potencies and that such additives could be used to ameliorate the HPNS effects in future human exposures.

Concurrently in England, an Oxford group led by Miller (1972), while investigating pressure reversal of anesthesia, developed a general hypothesis to account for both pressure reversal of inert gas narcosis and HPNS, based on the theory that "anesthesia occurs at constant volume fraction rather than constant mole fraction." The authors measured the anesthetic potencies (ED 50) of 4 gaseous and 5 liquid anesthetics in newts, using the abolition of righting reflex as their endpoints. They found the data to be consistent with their "critical volume hypotheses." Using this theory, they noted correlation between their theory and the observed anesthetic pressure of hydrogen, which is significantly higher than can be explained by the Meyer-Overton hypotheses. Further, they found their model predicts that, in the case of hydrogen, the gas-induced expansion is approximately balanced by pressure, which would make it the ideal oxygen diluent for very deep dives.

The three preceeding papers were important in extending the investigations of hydrogen into the high pressure range and providing the data and theoretical concepts with regard to narcosis and HPNS, which must necessarily be considered prior to any human exposures at very deep depths with this mixture.

Meanwhile at GERS, the French Navy group led by Michaud (Michaud et al., 1973) was also conducting animal experiments with somewhat different results. They reported a series of experiments on mice and rabbits exposed to hydrogen-oxygen breathing mixtures at 29 ATA for exposure times ranging from 30 min to 72h, at temperatures of 29°, 32°, and 34° C. In the short exposures, 0 to 2 h, significant EEG abnormalities were noted; however, the animals survived the exposure at maximum pressure. Some died during decompression, and the deaths were considered attributable to decompression. It was pointed out, however, that when the animals were exposed to the same decompression schedules following helium-oxygen exposures, the animals survived. The longer exposures resulted in diminution of EEG amplitude and finally death while at 29 ATA. The authors concluded that death was probably due to use of hydrogen. This paper unquestionably had a profound effect on future research on these mixtures.

While the French experiments were taking place, a research team led by Edel (Edel et al., 1972) was studying hydrogen decompression and making feasibility studies on this mixture for possible applications in commercial diving. Project HYDROX-I involved a series of human exposures ranging from 10 to 120 min at 200 FSW in a dry chamber. The decompression studies showed that decompression obligation was apparently greater for hydrogen than for helium. This was confirmed by decompression following exposure of a dog to 1000 FSW for 39 h. A decompression schedule which presented only slight problems upon surfacing following an equivalent exposure, using helium-oxygen, produced severe symptoms of decompression sickness in the same animal at 360 ft after exposure with hydrogen-oxygen mixtures. The finding that a decompression schedule which was satisfactory following a helium-oxygen saturation schedule could be lethal after the same exposure with hydrogen-oxygen offered a possible explanation for the animal deaths occurring during decompression in the French Navy experiment. More important, the animals had survived for 39 h with this mixture at 1000 FSW (total exposure time of 89 h under pressure with this mixture). However, special care had to be taken to maintain the temperature within a narrow temperature band having a center value of 31.5°C. This requirement was obtained by observing the response of the animals as chamber temperature was varied in initial phases of the experiment. This may offer a possible explanation between the contradictory results obtained by the American and French research teams, as well as the reason for selection of this paper.

Later, another team of investigators led by Edel (Edel, 1974) continued these studies in Project HYDROX II, in which a number of manned exposures were made with hydrogen-oxygen and nitrogen-oxygen mixtures for 2 h at 200 ft in dry chamber experiments. The comparative analysis of the decompression data made it possible to construct a mathematical decompression model for hydrogen which can be used for future work and explained apparent anomalies in earlier decompression results. Other studies in connection with this experiment included biochemical observations, mental performance tests, mass spectrometer studies, speech studies, Doppler Flometer monitoring, and pulmonary function measurements. The latter showed breathing resistance with hydrogen to be approximately 50% of that with helium, an important factor for exposure to very high pressures. The other results showed no significant difference when compared with helium, with the exception of decompression characteristics which were found to be midway between nitrogen and helium. The contributions of this paper represent another step in hydrogen-oxygen research.

HYDROGEN-OXYGEN DIVING

P. O. EDEL

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VOLUME 41, No. 3 NOVEMBER 1941

HUMAN PHYSIOLOGY UNDER HIGH PRESSURE

I. EFFECTS OF NITROGEN, CARBON DIOXIDE, AND COLD

BY E. M. CASE, M.A., PH.D. AND J. B. S. HALDANE, F.R.S.

UNTIL recently most work upon human beings under high pressure was concerned rather with the effects of changing pressure than those which occur when the pressure is kept constant. The most obvious effects of compression are pain in the middle ear and often in the sinuses. The latter, however, does not occur in most healthy people, whilst the former can be avoided by training in opening the Eustachian tube. Trained subjects can be very rapidly compressed. Later on the much more serious effects of decompression were noted. These can be avoided by stage decompression (Boycott, Damant & Haldane, 1908), and this in turn can be greatly accelerated if oxygen is breathed instead of air in the latter stages of decompression (Davis, 1935).

Besides effects such as those of cold and of poor air supply which can be readily avoided, two other effects appear at high pressure. One of these is oxygen poisoning. This is particularly dangerous when oxygen is breathed instead of air, as in some types of self-contained diving dress and rescue apparatus. We hope to publish results on this question later.

The second effect, which is now generally ascribed to nitrogen, seems to have been first described by Damant (1930). In his account of a discussion at the meeting of the British Association for the Advancement of Science in that year, he refers to Sir Leonard Hill's description of the mental and emotional abnormalities which occur even in picked divers at such depths as 300 ft. Sometimes such men on their return to the surface had no recollection of events prior to their ascent. High partial pressures of oxygen and impurities in the air were suggested causes of this phenomenon, but Hill's observations on the subject had satisfied him that neither oxygen nor carbon dioxide was responsible.

Phillips (1932) and Hill & Phillips (1932) considered the hypothesis that the behaviour of subjects under high-pressure conditions is to be explained on wholly psychological as distinct from physiological grounds.

Behnke, Thomson & Motley (1935) investigated the effects of air at 3 atm. and over, which they summarized as 'euphoria, retardment of the higher mental processes, and impaired neuro-muscular co-ordination', and they put forward for the first time the considered opinion that the operative factor was nitrogen (without excluding the rare inert gases). They believed that nitrogen acts on the nervous system by virtue of its high solubility coefficient in lipoid substances as compared with that in water. They recorded, however, the fact that the symptoms are immediate in their onset. It is noteworthy, incidentally, that the symptoms described by these workers seem decidedly

more profound in degree than those which we observed, of which an account is to be given. For example, in the (apparently) sole test which they carried out at 10 atm., stupefaction was recorded and the palpation of a person's pulse was stated to be a task attended by great subjective difficulty. The desirability of the use of an artificial gas mixture for divers and caisson workers was stressed, and it was suggested that nitrogen should be replaced by a rapidly diffusible, sparingly soluble gas with a low partition coefficient for lipoid/water systems. Helium was not specified, but was in fact the gas in contemplation. At that time its very high cost was an obstacle in the path of its adoption.

The proposal that helium might advantageously be substituted for nitrogen in gas mixtures for high-pressure work had already been made some years before. It seems to have originated with Elihu Thomson in 1919 and 1920, a fact to which attention was drawn by the worker in question in 1927.

Hildebrand, Sayers & Yant (1928) discussed the subject and remarked that as early as 1919 a patent had been applied for (by C. J. Cooke, of Washington, D.C.) regarding the use of helium-oxygen mixtures for workers under pressure.

It is important to realize that these and similar suggestions for the use of helium were made purely from the standpoint of shortening the time necessary for decompression without simultaneously increasing the liability to 'compressed air illness' in its various manifestations, which was known to be attributable to atmospheric nitrogen. It was not until attention had been drawn to the psychological results of working in compressed atmospheres, as in the communication of Damant cited above, and until the work of Behnke and his colleagues had made it likely that nitrogen was responsible for these effects, that helium began to be studied from the point of view with which we are mainly concerned in this paper. Now, in the opinion of Behnke & Yarborough (1938), the position is that 'the improved mental condition of the diver has supplanted the saving in decompression time as the most important expected advantage in using helium'.

Shilling & Willgrube (1937) studied mental and neuro-muscular reactions in compressed air in a quantitative way. Like all the American workers, they emphasize the 'stimulation and well-being' experienced by subjects at five or more atmospheres. They imposed a set of tests not uncomparable with, but perhaps rather more exacting than the ones we have used, and they observed deterioration in performance under pressure, with experienced as well as inexperienced subjects. In discussing the aetiology of the effects, they remark upon the facts that the greatest change is noticeable immediately on reaching the pressure, and that if a man is compressed too quickly he becomes unusually dizzy and dazed and requires some minutes to attain comparative normality. At present, as we ourselves agree, the nitrogen narcosis theory does not seem to offer a complete explanation of such facts.

End (1937), in a series of experiments primarily concerned with the

shortening of decompression times by the use of helium-oxygen mixtures, was also led to the conclusion that helium could be instrumental in freeing divers from the untoward psychological effects of air at high pressures.

The same author (1938) describes a world record dive (in 420 ft. of fresh water) made by Nohl in a suit of special design, breathing a helium-oxygen mixture. It is stated that mental symptoms were entirely obviated, though in view of the fact that the diver was a man of calm temperament and unusual intelligence, no sweeping conclusions are drawn.

Behnke & Yarbrough (1938), in a comprehensive study of helium from a physiological aspect, made a number of observations that are of interest in view of our findings, to be reported in this paper. The most striking bodily effect, they say, is the feeling of normality in contrast with the usual intoxication and sense of pressure and depth associated with high air pressures. At a pressure corresponding to 500 ft. of water, the subject felt well, and it appeared to him that he was at a depth of not more than 100 ft. At 300 ft., when air was suddenly supplied to a diver breathing helium, dizziness and loss of muscular control were produced, together with a sensation of 'floating away'.

Behnke & Willmon (1939) observed mental disturbance in divers working at 240 ft. in the salvage of U.S.S. *Squalus*. The authors were surprised at the unusual intensity of the symptoms that occurred, and their communication is of interest because they found an accumulation of carbon dioxide in the divers' helmets. The symptoms, nevertheless, were not typical of high carbon dioxide concentration in the lungs, but rather of air at pressures higher than actually obtained. Their conclusion was that the increase in carbon dioxide tension augmented the narcotic action of the nitrogen; and it is stated in support of this that such symptoms can be decreased by lowering the carbon dioxide by excessive ventilation. The troublesome symptoms in this series of operations were overcome by the substitution of helium-oxygen mixtures for air.

It was the object of the experiments here recorded to confirm the work of the American investigators on nitrogen narcosis, and also to investigate the concomitant effects of carbon dioxide and cold. For at 10 atm. pressure a carbon dioxide concentration of 0·5% gives a partial pressure of 5%, which may be expected to have some physiological effect. And the sea water at a depth of 300 ft. is often much colder than the surface water. For these reasons Admiral Sir M. E. Dunbar-Nasmith's physiological subcommittee for saving life from sunken submarines asked us to furnish information on the subjects discussed in this paper, and some others, while Messrs Siebe Gorman and Co. were so kind as to place their equipment and the services of their staff at our disposal.

METHODS AND PERSONNEL

All the experiments were conducted in a cylindrical steel chamber of 100 cu. ft. capacity. Its horizontal length is 8 ft., its diameter 4 ft. Thus two subjects can use it at a time. The experiments were done on E. M. C. and

J. B. S. H. together, or on another subject, with one of them acting as an observer. The only experiment in which one of us went in with two others was unsatisfactory, as one of the subjects became obstreperous, and interfered with tests carried out by the other. Lighting is through windows from the outside. There is no telephone, but communication took place by a code of taps, by messages shown at the windows, and by shouting. The pressure was raised by air from cylinders outside. CO_2 was added from cylinders of liquid CO_2 inside, besides what was produced by the subjects. Air samples were taken in the chamber, and analysed later with the Haldane apparatus at atmospheric pressure. Owing to the small size of this chamber, subjects could not stand, and it is conceivable that this may explain some of the differences between our results and those of the American observers.

Decompression was carried out in accordance with the tables published in Davis's *Deep Diving* (1935). It was facilitated by breathing O_2 at pressures of 3 atm. and less. In this way the time needed for decompression after 16 min. stay at 300 ft. of salt-water pressure (10 atm.) is reduced to only 59 min. Our only deviation from the tables, except where the contrary is stated, consisted in the fact that we added half the period of compression, instead of the whole of it, as recommended, to the time spent 'at the bottom'. The O_2 used in the later stages was supplied from cylinders in the chamber, and breathed from the 'Salvus' apparatus in which the CO_2 expired is absorbed by soda-lime.

As a test of manual skill we used the R.-V. Manual Dexterity Test, supplied by the National Institute of Industrial Psychology. A number of steel ball bearings must be placed in three holes. During a first period of 1 min. they are picked up with a forceps and placed in the first hole, during a second minute they are placed in the second hole with a scoop, and during the third in the third hole with finger and thumb. The subjects were always given a preliminary test before their first recorded test in the chamber at atmospheric pressure. A typical score was $21+14+25=60$, the second minute's work being almost always the most difficult. The scores varied considerably both between individuals and with lighting, seating, and other arrangements; but we were only concerned with the differences produced by the pressure change.

As a test of intellectual ability we gave a series of four-figure multiplications, e.g. 9746×4956. Rapid calculators could do ten such in 6–8 min. Others were required to do five to eight only. The time taken and the number correct were recorded. The subjects were also encouraged to take notes, and these latter afforded valuable evidence of their mental condition and muscular co-ordination.

In experiments where CO_2 was added, E. M. C. or J. B. S. H. often breathed through a canister containing soda-lime, whilst observing the other subject. However, owing to the intoxicating effect of the N_2, this precaution was sometimes omitted, and for the same reason the observations were sometimes

imperfect. An external observer watched through a small window, but could only note the more striking symptoms of those within.

The following subjects were used. The age is given in each case. Jermyn and Spurway are females:

W. Allen, 30.
S. Callaway, 24.
E. M. Case, 35.
O. Daniel, 23.
J. B. S. Haldane, 47.
T. S. Hardie, 31.
J. E. Jermyn, 24.
H. Kahle, 41.
H. Kalmus, 34.
J. Larmour, 30.
B. Matthews, 36.
J. Millie, 34.
J. Negrin, 48.
J. Prendergast, 26.
J. M. Rendel, 25.
H. Spurway, 25.
R. Winfield, 30.

The majority are English, but two are Irish, one Spanish, one Czech, and one German. Their occupations had varied from prime minister to tailor, and loader for a transport company. The majority are, however, university graduates.

MECHANICAL EFFECTS OF COMPRESSION AND DECOMPRESSION

Though our main object was not to study the effects of compression and decompression, our observations thereon are not without interest. During compression all subjects noticed slight pain in the ears, and a few of them in sinuses. We were, however, surprised at the ease with which most of them could be compressed, even at the first trial, after being told how to force air into the Eustachian tubes by holding the nose and blowing. Unless suffering from a cold, it was exceptional for a subject, even at the first attempt, to require as long as 6 min. for compression to 10 atm.

In view of a suggestion that men without biological training might find difficulty in inflating their Eustachian tubes, we paid special attention to four working-class subjects. Each was shown how to compensate for rising pressure by holding his nose and blowing, and allowed to stop the compression if he felt pain. The longest time taken to reach 10 atm. was 5 min.

Our three most difficult subjects were B. M., J. N., and H. Ke. B. M. had a fairly severe cold, and, although he used a benzedrine inhaler, took 9½ min. to reach 10 atm. J. N. had trouble with his left ear, and several stoppages were necessary before 10 lb. pressure (1·7 atm.) was reached. Then some obstruction appeared to give way, and a pressure of 10 atm. was reached in 11 min. H. Ke. had had both eardrums burst by shell fire in 1917, and in his first experiment it took 26 min. to compress him to 8·6 atm. He was later given several educational compressions to 2 atm., and found that swallowing was more effective than nose-blowing in opening his Eustachian tubes. At the time of writing he still requires about 10 min. for compression to 6 atm., but seems to be improving rapidly.

We think that the vast majority of subjects could be trained to adjust rapidly, but it is important that instructions should be given tactfully and that the subjects should have full confidence. We and our trained subjects can be compressed to 10 atm. in $2\frac{3}{4}$ min., and were apparatus available, could certainly be compressed much quicker. Even with a severe cold E. M. C. had no difficulties during compression, but had sinus and ear pains during decompression.

The quickest compression recorded is from 1 to 7 atm. in 90 sec. This caused no after-effects, and no appreciable discomfort. It corresponds to a descent of 133 ft. per min. in sea water, which is near the record for a diver. The absolute rate of pressure increase, of $\frac{1}{2}$ atm. in $7\frac{1}{2}$ sec., corresponds with that which would be experienced by the pilot of an aeroplane diving vertically from some 18,000 ft. to ground-level in $7\frac{1}{2}$ sec., that is to say at over 1600 miles/hr. Clearly therefore trained and picked pilots are not likely to suffer from this cause for many years to come.

We had one serious casualty. J. M. R. was thrice compressed to 8·6 atm. (250 ft.) in the course of a month. One or two hours after the first experiment he noticed a pain referred to the left axilla which he attributed to 'indigestion' following a meal. The second experiment had no such effect. The third caused a return of the pain, and shortness of breath. These symptoms persisted, and 16 days later he was examined by Dr A. Morland, of University College Hospital. He found 'signs of pneumothorax on the left side, the heart being displaced about $1\frac{1}{2}$ in. to the right. X-ray examination confirmed the presence of the left-sided pneumothorax. It also showed three thin-walled cavities having the appearance of emphysematous bullae at the extreme right apex. There was no evidence of tuberculosis.'

He was admitted to hospital, and found to be free from symptoms except those directly due to the pneumothorax. Twenty-three days after the last experiment Prof. R. S. Pilcher carried out a thoracoscopy at Leavesden Hospital under local anaesthesia. He reported as follows:

'The left lung was found to be nearly fully collapsed. No bullae were seen on the surface nor any stumps of adhesions. The apex of the upper lobe had a curious notch in the upper border of the lobe. This notch was whitish in colour, and in a groove running along it was what looked like a small blood clot. On the lung below the notch was a narrow band of fibrin. This appearance may have been due to a ruptured bulla, but no others were seen. The patient inhaled cigarette smoke during the examination, but no escape into the pleura was seen. There was no blood or fluid in the pleura.'

The patient made a slow but uneventful recovery. Five months after the first experiment there was a slight relapse. J. M. R. felt bubbles in the right side, but no pain. An X-ray examination showed a small bubble of air in the pleural cavity, which disappeared spontaneously. Eight months after the first experiment there was a more serious relapse. The left lung collapsed completely. Prof. Pilcher performed a thoracoscopy and found that an

adhesion had given way. He then blew in fine-grained talcum powder, producing a sterile inflammation which caused the lung to adhere to the pleura. It is hoped that this will prevent any further relapse.

Dr Morland has little doubt that J. M. R. suffered from a rare congenital condition, in which weak areas are present in the lungs. J. M. R. was an athlete, and had had numerous routine examinations of the lungs, but no X-ray examination with special reference to this condition.

The immediate cause of the rupture is not clear. Any of the following would seem to be possible:

(*a*) The lung was over-distended while inflating the Eustachian tubes during compression.

(*b*) The subject held his breath during a decompression, and the expansion of the air brought about the rupture.

(*c*) During one of the later stages one of us turned on the by-pass of the 'Salvus' apparatus too rapidly and fully, thus causing a sudden increase in the gas pressure in the lung. One of us has himself experienced a definite though transitory pain from this cause.

(*d*) A bulla with poor communication with the bronchi existed and filled up with air at high pressure. During decompression the air could not escape into the bronchi, and burst out into the pleura. However, the communication with the bronchi was sufficient to allow leakage.

In the absence of further information we cannot distinguish between these hypotheses.

Before we were convinced of the validity of the nitrogen narcosis theory we made some observations on the circulation. They are somewhat incomplete, and since they are probably in part due to the effects of high-pressure O_2 they will be discussed in a later communication. It is sufficient to state that there were no changes either in pulse rate or systolic pressure which could possibly account for the symptoms described later. Both rate and pressure rose in some cases and fell in others, the changes in subjective feelings and behaviour being nevertheless much the same in the two cases.

Besides this, E. M. C., J. B. S. H. and H. Ke. had fillings in teeth loosened, and J. B. S. H. lost a dead tooth which had been quiescent since 1906, but began to hurt during decompression, and developed an abscess. Such effects are well known both in divers and aeroplane personnel.

The usual effects of pressure on the voice were noticed. When E. M. C. was compressed to 10 atm. during an attack of laryngitis, he found speech much easier at pressures above 4 atm. The effect of H_2 and the similar effect of He on the timbre of the voice persisted at 10 atm., though less striking than at atmospheric pressure. At 320 ft. (10·7 atm.) a cylindrical flageolet ('tin whistle') required greatly increased effort to blow it. The pitch was unaltered, but the tone was fuller and rounder than normal, rather like that of a recorder, and the second octave was difficult to execute clearly. The pitch of an oboe reed was much reduced, and a tuning-fork gave its normal note. At high

pressures loud cracking noises, audible to others, were frequently produced when J. B. S. H. moved his shoulder joints. Clearly the pressure between the articular surfaces is increased tenfold, and the effect of irregularities must be enhanced. No pain was associated with these sounds. J. N. noticed 'strange sensations on the lips, something like velvet'. J. B. S. H. noticed them on several occasions subsequently. We have no explanation to offer.

A point of some practical importance was noted in connexion with breathing apparatus. Whilst observing the reactions of others in mixtures containing much CO_2 under high pressure, E. M. C. and J. B. S. H. were provided with mouthpieces attached to canisters containing soda-lime, to remove CO_2 from the inspired air. The resistance of these became very large. For the volume breathed per minute remains approximately constant when the pressure is raised, whilst the mass per minute is proportional to the pressure. Thus, if other things are equal, the work done per minute in breathing is ten times as great at 10 atm. as at 1 atm. But other things are not always equal. At high pressures, flow through an orifice becomes turbulent at velocities which do not give turbulence at a lower pressure. If so, resistance rises a good deal more than ten times.

Not only did the resistance of certain canisters become unbearable, but they gave off caustic dust which caused coughing, though they had not done so at atmospheric pressure. This is explicable if turbulence set in. As a result of this resistance, coughing, and particularly the lack of self-control caused by N_2, both of us, but particularly J. B. S. H., tended to remove our respirators, or not to put them on after speaking to other subjects. Our observations were often faulty, and we sometimes lost consciousness when this was not intended.

It is very desirable that all breathing apparatus intended for use at high pressure should be tested at that pressure. We wish, however, to state that in the Davis Submarine Escape Apparatus tested by us there was no unpleasant resistance even at 10·7 atm. (320 ft.).

Effects of decompression

When we adhered to Davis's tables the symptoms noted were generally slight. Most subjects complained during decompression on one occasion or another of itching, often accompanied by a slight rash. Both itching and rash disappeared after an hour or so at atmospheric pressure. Three subjects had nose bleeding during decompression. In one it was repeated. In the other two it only occurred once in a series of experiments.

It is possible that the rash and the nose bleeding are related, both being due to extreme dilation of the skin vessels. They can hardly be due to numerous small air embolisms, or they would be accompanied by more serious symptoms. They may possibly be due to impulses from posterior roots, similar to those causing 'bends' which are at least partly of central origin. However, we are not prepared to offer any definite explanation.

When the tables were adhered to, only four subjects out of fifteen, namely, T. S. H., J. E. J., H. Ke. and H. S., had bends. The pain was localized in the arms or more rarely in the legs, and was fairly severe in T. S. H. and H. S., sometimes lasting till the next day. H. Ke. is fairly fat, but not so fat as J. N. and J. B. S. H. J. E. J. and H. S. have the subcutaneous fat normal to their sex, but no more, whilst T. S. H. is definitely thin. So there is no obvious correlation with fatness.

When the tables were not adhered to, bends were more frequent. Thus J. B. S. H. and H. Ke. took 26 min. to compress to 8·6 atm. (250 ft.). They remained for 32 min., and were decompressed according to a schedule calculated for 45 min. stay at 250 ft. Both developed bends, H. Ke. rather severely, but J. B. S. H. slightly. J. B. S. H. also developed slight bends after an experiment at 8·6 atm. 3 days later in which the time table was adhered to. He did not develop them in any of over thirty later experiments at 8·6 atm. and above.

Subjects B. M. and R. W., who are attached to the Royal Air Force and wished to experience bends, were compressed to 10 atm. in 9½ min., and after remaining at this pressure for 7½ min. were decompressed in accordance with the time table for 12 min. at 300 ft., which assumes oxygen breathing from the 60 ft. stage to surface. However, neither breathed it, though J. B. S. H. who was with them, supervising the experiment, did so. B. M. developed pains in the buttocks and neck, and had somewhat impaired vision during the latter part of the decompression. On emerging, the pain became worse, and spread to the shoulders. R. W. had no symptoms other than itching and fatigue. B. M.'s symptoms disappeared after about 2 hr.

E. M. C. has on several occasions breathed air instead of O_2 during one to three stages of the decompression, without experiencing bends or other untoward symptoms. On three occasions he has breathed air throughout while being decompressed in accordance with the O_2-breathing schedules. The first of these was after 8 min. at 10 atm., for 4 min. of which period he had been breathing a H_2-O_2 mixture. There were no symptoms. The second was after 10 min. at 7 atm. in air, and slight bends in one elbow and wrist resulted, lasting for a few hours. The third occasion was a decompression (from 20 min. at 10 atm.) during which air had been breathed. The decompression lasted for 86 min. Distinct but not severe pains in both hips and shoulders developed immediately on emerging, and lasted for some 48 hr., together with a slight general feeling of malaise.

It is clear that individuals vary greatly in their susceptibility, and probably somewhat from day to day. The schedule is not quite satisfactory for some persons, notably H. S. and T. S. H. It could be greatly shortened for E. M. C. and R. W. Indeed, for the latter the time could probably be halved. It is very possible that even the susceptible persons would have escaped, had they taken vigorous exercise during decompression, as recommended. This is difficult in the small chamber used.

As related later, a mixture of 85% He and 15% O_2 was breathed on several occasions by E. M. C. and J. B. S. H. After breathing this for 11 min. at 10 atm. in a self-contained apparatus, O_2 being added from a cylinder and CO_2 absorbed by soda-lime, J. B. S. H. was decompressed according to the usual schedule. He noticed no itching during decompression. But on emerging there was severe pain in the right hip and both shoulders, becoming worse on moving; and itching of the back. An hour later there was also severe pain in the buttocks, and a burning pain in the skin of the left scrotum and thighs, later spreading to the calves.

Next day there was itching over a nearly symmetrical area reaching in the sagittal plane from the back of the scrotum to near the base of the coccyx, and laterally as far as the ischial tuberosities, rather farther on the right. He was constipated for 3 days, and then had burning pain on wiping the anal mucosa. These symptoms persisted for 3 weeks, and then abated, but after 6 months there was still itching and some anaesthesia over the coccyx. The original distribution of the itch corresponds to that of the 4th and 5th sacral roots, the distribution after 6 months to that of the 5th sacral roots. Dr E. A. Carmichael suggests that the lesion, presumably caused by a bubble, is located near the tip of the conus.

E. M. C. repeated the experiment, breathing the He-O_2 mixture for 19½ min. including the first 9 of decompression, and then changing to O_2. He had no symptoms. J. B. S. H. therefore breathed the mixture at 10 atm. for 9 min., and for the first 6 min. of decompression. To his relief he had no symptoms beyond a faint itch on the forearm.

The result is therefore inconclusive. All that can be said is that out of some forty decompressions from 8·6 or 10 atm. the only occasion on which J. B. S. H. had serious bends, when adhering to the schedule, was after breathing a mixture where He was substituted for N_2. It is difficult to suppose that this was quite fortuitous. And it is certain that a mixture of this kind cannot be regarded as superior to air as a prophylactic against bends, as has been claimed by some, but not all, American workers.

In a number of experiments, as related below, CO_2 was added to the air breathed at 10 atm. This caused hyperpnoea, and probably vasodilation. During decompression the partial pressure of CO_2 fell, so that there was no hyperpnoea and presumably no vasodilation. We expected that in consequence more N_2 than usual would be absorbed at the high pressure, and no more given out during decompression, and hence that bends would occur. However, no one developed bends under these conditions except H. S. and J. E. J. The former had had them without CO_2, and did not develop them after breathing the largest concentration of CO_2, which made her unconscious. The latter has not been tested without CO_2. It appears, therefore, that CO_2 does not appreciably increase the incidence of bends.

Our longest stay at 10 atm. pressure was 30 min. We were compressed in 4 min., and the decompression took 2 hr. 39 min.; during the last 2 hr. and

10 min. we breathed O_2. In general we did not stay for more than 12 min. at this pressure, decompression lasting for an hour.

NITROGEN INTOXICATION

Only ten subjects were subjected to high pressure without the addition of carbon dioxide. However, it will be seen that many of the effects observed when carbon dioxide is added are N_2 effects.

E. M. C. and J. B. S. H. can barely notice anything abnormal at 5 atm. (130 ft.). At 6 atm. there is a slight but definite change in the consciousness, which is marked at 8·6 atm. (250 ft.) and very strong at 10 atm. (300 ft.) Most of the experiments were done at these two latter pressures. At 6·3 atm. (177 ft.), in a single experiment the total score in the skill test fell from 143 to 140. The mean time of the arithmetic test fell from 8 min. 11 sec. to 6 min. 51 sec., and the mistakes from 6 out of 20 to 3 out of 20. Thus there was no evidence whatever of deterioration. In view of the results of American workers, it is, of course, possible that others might have been more affected; however, E. M. C., J. B. S. H. and H. Ke. are pretty normal at 7 atm.

Seven subjects were tested at 8·6 atm. (250 ft.). E. M. C. and J. B. S. H. were slightly confused. Two others were distressed, and felt as if they were going to faint. One was euphoric and talkative, feeling very confident, another mildly elated. The fifth was perhaps unusually obstinate, but showed no obvious emotional reaction. The mean score of five subjects in the manual dexterity test was 64·8 at atmospheric pressure, 66·0 at 8·3 atm. The difference is insignificant. In two subjects a further test after 24 min. under pressure showed no deterioration.

The results of the arithmetic tests were very different. The time taken was generally, but not always, increased. In four subjects the number of mistakes increased from six to twenty-two in a total of thirty-three sums. One subject (H. S.) was exceptional in making only one mistake out of six in each series, though under pressure she had to do her arithmetic aloud.

Five subjects were tested at 10 atm. (300 ft.). The results on eleven subjects at 10 atm. pressure with additional CO_2 are reported later. E. M. C. and J. B. S. H. were somewhat euphoric on the first occasion, but later on this wore off; however, both, and especially J. B. S. H., always tended to make notes which were intended to be humorous, and were sometimes improper. They were always rather confused. J. N. preserved complete outward calm. R. W. laughed a good deal, and 'cheated' in the dexterity test. B. M. varied between depression and elation, at one moment asking to be decompressed, because he felt 'b... awful', and the next laughing, and attempting to interfere with R. W.'s dexterity test. E. M. C. and J. B. S. H. had a mean score of 79·2 at atmospheric pressure and 72·4 at 10 atm. in a total of five experiments. Before one pair of these they had taken 15 and 10 mg. benzedrine respectively. Their scores after this were higher throughout, but fell slightly under pressure. $t=3{\cdot}16$ for 4 degrees of freedom. The probability that this

is due to chance is about 0·04. But J. N.'s score rose from 54 at 1 atm. to 55 at 10 atm. R. W. also increased his score from 57 to 60, but was detected 'cheating', i.e. picking up two balls at a time, although he is a responsible scientist at atmospheric pressure.

The arithmetic was probably worse than at 8·6 atm. E. M. C. made ten mistakes out of twenty, J. B. S. H. nineteen out of twenty-one, as compared with normal values of three and five mistakes out of twenty, respectively. B. M. completed one sum in 12 min. This was wrong.

Perhaps of even greater importance are the observations made on our practical activity and judgement. J. B. S. H. was more affected than E. M. C., but both found it hard to carry out several different tasks; for example, timing a test on another subject, taking notes, and taking gas samples. For this reason several arithmetic tests were not timed, and other observations were not as satisfactory as could have been wished. Thus J. B. S. H. noted down a failure to press the button of the stopwatch as 'forgot to turn tap'. It is quite imperative that no great trust should be placed in human intelligence under these circumstances. For example, J. B. S. H. poisoned himself with O_2 and had severe convulsions through a mistake which would have been unpardonable at atmospheric pressure. Handwriting generally deteriorated.

In a single experiment at 10·7 atm. (320 ft.) E. M. C. and J. B. S. H. felt no worse than usual, and were able to make observations. It is quite incorrect to say that people are stupefied at such pressures, as will come out even more forcibly when the effects of adding CO_2 are considered. However, they are definitely less responsible than when normal.

Subjectively many subjects reported that they felt drunk. J. B. S. H. felt somewhat mystical. His consciousness was invaded by words, sometimes nonsensical and always irrelevant, which appeared to him to be very important at the time, and by memories of childhood. H. S. not only felt all sensations as abnormal, but had a strong conviction of sin, and of the necessity of divine grace. The subjective symptoms were already beginning when 'bottom' was reached, were maximal within 2 min., and no worse after 30 min. at 10 atm. We have the impression that there is a slight degree of habituation. However, we have no objective evidence for this. And if it exists it may be purely psychological. On a first compression the change of consciousness is very striking, and alarms some people. When it is taken for granted, it is likely to have less effect on behaviour.

On decompression there was almost always an immediate feeling of subjective improvement when the pressure was reduced to 5 atm. 'I feel normal again', 'Erholt sich alles', and 'My god, I'm sober', are typical notes. The handwriting and arithmetical ability improved. It is clear that the main effect of the high pressure was on the higher functions of the brain, intellectual and moral performance being much more affected than muscular skill.

A canary was not merely able to stand on its perch, but to fly round the chamber, and alight satisfactorily. This is of interest, since the increased

density of the air was obvious to human observers moving their hands. On the other hand, *Drosophila melanogaster*, a small fly, walked but would not fly, even when mechanically stimulated.

Our experiences with mixtures containing He and H_2 leave us in no doubt that our symptoms were due to N_2. It is, however, possible that this gas may act by interfering with oxidation in the tissues. If this interference occurs at an early stage, there should be antagonism between N_2 and O_2, and the symptoms at a given partial pressure of N_2 should be worse if that of O_2 is lowered. In air at 10 atm. the partial pressure of O_2 is 2·1 atm. A mixture of 98% 'nitrogen' (atmospheric) and 2·3% O_2 was therefore stored under pressure, and breathed through non-return valves. At atmospheric pressure it naturally caused asphyxia in both of us. At 8·6 atm. this mixture had a partial pressure of 8·4 atm. N_2, as compared with 7·9 in air at 10 atm., and 20% of an atmosphere of O_2, as in air at a pressure of 0·94 atm. J. B. S. H. breathed it for 17 min., and retained consciousness, but made five out of five arithmetical mistakes. E. M. C. breathed it for the last 7½ min., but felt no change of consciousness on doing so. However, as he attempted to blot his pencilled notes, he was by no means normal. In another similar experiment the mixture contained only 1·5% O_2, so that the partial pressure of O_2 was 12·9%. J. B. S. H. breathed this for 6 min., and E. M. C. for 8 min. Both had hyperpnoea, and felt worse than in ordinary air, the former feeling much better on breathing air at 8·6 atm. Neither lost consciousness, and J. B. S. H.'s score on the dexterity test was only reduced from 70 to 53. It is, we think, clear that there is little synergism between N_2 excess and O_2 shortage.

The following incidental observation was made. J. B. S. H. usually and E. M. C. once or twice noted a peculiar taste. A number of other subjects did the same, and one noticed a smell. The taste was variously described as metallic, harsh, salty, and indefinable. It was noted when the O_2 pressure had not been raised. Moreover, at 3 atm. pressure O_2 has no taste, though J. B. S. H. constantly, E. M. C. once, and H. Ks. on the only occasion when he was tested, have noted an astringent and slightly sweet taste confined to the back or the lower surface of the tongue when breathing it at 5 or 6 atm. Thus the harsh or metallic taste is probably that of N_2.

EFFECTS OF BREATHING MIXTURES WHERE HELIUM OR HYDROGEN IS SUBSTITUTED FOR NITROGEN

A mixture containing 85% He and 15% O_2 was prepared and compressed in a cylinder. This was let into a Douglas bag, and rebreathed through a canister absorbing CO_2. It was renewed from time to time to avoid O_2 want. E. M. C. first breathed O_2 for 12 min. at atmospheric pressure to get rid of N_2, then washed his lungs out repeatedly with the He-O_2 mixture, and was compressed to 10 atm. He felt no trace of discomfort apart from heat due to adiabatic compression. He made one mistake out of ten sums, but noticed

a twitching of the lips, which passed off, and was not noted in later experiments. After 10 min. at 10 atm. he began to breathe air. His voice was thin and nasal. There was no instant subjective effect, but after 2 min. he felt 'slightly cock-eyed', and after 3 min. had the full subjective symptoms. J. B. S. H. did not start breathing the mixture till 10 atm. pressure was reached. He felt a great relief of his symptoms, and his arithmetical performance was normal. After 5½ min. he started breathing air. There was a slight feeling of giddiness after 1¼ min. and a marked change of consciousness after 2 min.

In two later experiments on J. B. S. H. and one on E. M. C., the same mixture was used, but it was placed in the bag of a Davis Submarine Escape Apparatus and rebreathed, O_2 being added at a rate of 130 c.c. per min. from time to time. J. B. S. H. began breathing the mixture at atmospheric pressure. At 10 atm. he felt slightly abnormal for a short time, perhaps because he had got rather short of O_2, preferring the risk of asphyxia to that of convulsions. He could, however, do mental arithmetic such as 97×43 correctly after 8 min. After this experiment he had the nervous symptoms described above. In a similar experiment E. M. C. began breathing the mixture on reaching 'bottom' (10 atm.) and noted a subjective change for the better in 1 min. Another experiment on J. B. S. H. designed to test decompression effects produced a similar result.

We next proceeded to substitute H_2 for N_2. A mixture of 4 vol. of H_2 with 1 vol. of O_2 is highly explosive, so that its physiological properties would only be of theoretical interest. However, according to information kindly given to us by Prof. A. C. G. Egerton, Secretary of the Royal Society, H_2-O_2 mixtures do not explode at 10 atm. if they contain over 96% of H_2, nor H_2-air mixtures if they contain over 68·7% of H_2. A mixture of one part of air with nine of H_2 is therefore entirely safe, and yet, at 10 atm., it contains as much O_2 in a given volume as the same amount of air at atmospheric pressure. We filled two Douglas bags with air at atmospheric pressure, and added H_2 from a cylinder during and after compression to 10 atm., mixing the contents thoroughly. We then breathed the mixture through non-return valves. J. B. S. H. breathed it for 6 min., E. M. C. for about 4 min. J. B. S. H. made one mistake in four sums, perhaps because the gas rising in front of his eyes made writing difficult. Both felt normal, but found the mixture unpleasantly cold. We are not in a position to compare the physiological effects of He and H_2. To do so it would be necessary to carry out experiments at 20 or 30 atm., where one or both of them may begin to have an effect.

Behnke & Yarbrough (1939) report that the narcotic effect of A is somewhat greater than that of N_2. A single experiment on E. M. C. in which A was substituted for the N_2 in air at 6 atm. led to a deterioration in the manual dexterity test, but no noticeable subjective changes. Nor did bends develop on decompression according to the usual schedule. Thus our observation, so far as it goes, confirms Behnke & Yarborough.

These experiments leave no doubt in our minds that Behnke *et al.* (1935)

were entirely correct in ascribing the effects of compressed air on consciousness and behaviour to its N_2 content, even though we differ from them slightly as to the effects found. But it is far from clear to us which are the relevant properties of the gases in question. Our experience with resistant canisters rules out the possibility that the good effect of He when replacing N_2 under pressure can be due to diminished respiratory resistance, which probably accounts for its good effect on asthma. On changing from one gas to another, the subjective change takes several minutes to develop. Hence they cannot be due to the physical properties of the gases in the gas phase. Nor can they be due to their rates of diffusion when dissolved, as the symptoms due to N_2 reach their maximum after about 3 min. The differences between different gases must, we think, be due to their activity or inactivity in the brain tissue itself. The following solubilities at 38° C. are taken from Behnke & Yarbrough, and from Seidell's (1940) tables:

Gas	H_2O	Olive oil	Benzene
H_2	0·0165	—	0·076
He	0·00872	0·0148	0·021
N_2	0·01275	0·0667	0·116
A	0·0262	0·1345	0·222

It is at once clear that solubility in water cannot be the decisive property, for H_2 is more soluble than N_2. The data on solubilities in oils are not quite comparable, but the following facts are to be noted. The solubility of H_2 in cotton-seed oil and train oil is about 0·04 at 100° C. and 0·055 at 180° C. Thus at 38° C. it is probably about 0·03 (Ubbelohde & Svanoe, 1919). The solubilities in human fats are probably of similar magnitudes, and that of N_2 not more than double that of H_2. The solubilities of these gases in heavy naphtha and gas oil (hydrocarbon mixtures) have been directly compared, that of N_2 being about 0·10, of H_2 0·07. If the solubilities in fat were in the same ratio, and the narcotic effects proportional to them, the effect of 9·8 atm. of H_2 would be the same as those of 8·7 atm. of air, which is certainly not the case. Even if the solubility of H_2 were only half that of N_2, we should expect the same degree of narcosis as in air at 6·2 atm. We are inclined to doubt whether this is so, though the effects which we observed at this pressure of air were very slight. On the whole, then, our results do not favour the theory that the narcotic effect of 'indifferent' gases is proportional to their lipoid solubility.

We clearly cannot ascribe the narcotic effect of N_2 to chemical properties, since A has none. But other physical properties are very different in H_2 and He on the one hand, and N_2 and A on the other. Thus Armstrong (1908) found that a particular charcoal at 0° C. adsorbed 4 vol. of H_2, 2 vol. of He, 15 vol. of N_2, and 12 vol. of A. It is at least possible that adsorption on surfaces within or on the cell may be as important as lipoid solubility in determining the narcotic properties of gases.

Carbon dioxide at atmospheric pressure

Several observations were incidentally made on the effect of CO_2 at atmospheric pressure. They are given here for comparison with its effects under pressure. In five experiments on various subjects the mean skill test score without CO_2 was 81·4, in 3–4% CO_2, 82·4. The mean percentage of arithmetical mistakes fell from 32 to 24. Neither change is significant, but clearly this amount of CO_2 has no bad effect, though it causes quite noticeable hyperpnoea. With about 6% of CO_2 J. B. S. H. and E. M. C. also found a slight but insignificant improvement in their performance at both tests.

These tests were made after a few minutes' exposure to the CO_2. However, there is little cumulative effect of CO_2 after several hours. Thus in another experiment where the partial pressure of CO_2 was gradually rising from 5·2% at 9 a.m. to 6·8% at 12.40 p.m., J. B. S. H. was able to do CO_2 analyses up to the end, the results checking with one another and the arithmetic being correct, although there was violent panting throughout this period, and some headache, photophobia, and nausea towards the end. The total pressure on this occasion was 1·1 atm. On other occasions this subject has carried out gas analyses in 7½% CO_2.

Thus CO_2 at 6–7% causes relatively little mental impairment or deterioration of manual skill, though most, if not all, people find it distressing. There is, of course, a slight degree of impairment of both manual and mental work, but the latter at least is far less than that produced by air at 10 atm. pressure.

Combined effects of carbon dioxide and pressure

This has been tested on eleven subjects, some of them on a number of occasions. In all but two cases the pressure was 300 ft. (10 atm.). The procedure varied. In a few cases CO_2 was not added till after the high pressure had been reached. In most experiments some at least was added before or during the compression, so as to ensure thorough mixing, whilst more was often added afterwards, the subjects stirring the air to the best of their ability. Analyses seemed to show that mixture had generally been pretty complete.

Breathing increased noticeably whenever the partial pressure rose above 3%, that is to say, at 10 atm., when the percentage rose above 0·3. But even with partial pressures of 6–8%, although there was panting, there was much less subjective distress than at atmospheric pressure, where the desire to breathe may dominate the consciousness. This lack of distress can probably be attributed to the narcotic effect of the nitrogen.

In six experiments (three of them on H. S.) the partial pressure was raised to about 4% at atmospheric pressure, and the subjects tested. Air was then added rapidly to bring up the pressure to 250 ft. in two experiments and 300 ft. in four. The partial pressure of CO_2 thus remained constant, save for that added by respiration, and may even have fallen when the observer was

breathing through a CO_2 canister. The subject was then retested during the 15 min. which was the longest time spent under pressure. The mean score in the manual dexterity test at 1 atm. was 80·5, at 8·6 or 10 atm. 51·9. Fisher's t test of significance is 3·02, hence the probability that the decrease is due to chance lies between 0·05 and 0·02. In five of these experiments the arithmetic test was also used. In one the subject remained staring at the paper for 7 min. and wrote down two digits, one of which was wrong. Among those who completed it the mean percentage of mistakes rose from 28·1 to 74·4.

Four subjects were compressed from 1 to 10 atm. (300 ft.), CO_2 being added during the ascent. The partial pressure of CO_2 varied from 3·6 to 4·3%. Manual dexterity tests were then done for comparison with controls at atmospheric pressure without CO_2. The mean score fell from 59 to 43·8. $t=3·49$, so once more the probability of a chance explanation lies between 0·05 and 0·02. In two experiments the partial pressure of CO_2 at 1 atm. was much higher, and air was added to make up 10 atm. The partial pressures of CO_2 at this total pressure were 6·3 and 7·5. The mean manual dexterity score fell from 78·5 to 55. One subject attempted the arithmetic test without being able to complete a single sum.

A number of other experiments gave the same result, namely, that the combined effects of high partial pressures of N_2 and CO_2 were much more severe than those of either alone. It will be realized that the observer was in the chamber with the subject, and had not only to add CO_2, take notes and samples, but also to supervise the tests. As a result of the increased resistance referred to earlier, and also of the effects of N_2, both observers, and especially J. B. S. H., tended to remove their respirators, or not to put them on again after speaking to the subjects. They would not have done this at atmospheric pressure, owing to the much greater subjective distress caused by a given partial pressure of CO_2. As a result their observations were often faulty, and they sometimes lost consciousness. However, another observer was stationed at the window, and it was generally possible to make out what had happened, even if notes were inadequate.

At higher partial pressures of CO_2 consciousness was lost. In almost all cases this took place quietly and easily. The subject remained sitting, leaning forward with his or her mouth and eyes open, and a glazed expression, and often salivating profusely. During the first stage of decompression consciousness was rapidly regained, and the subject could often begin writing within a few seconds, though he was subnormal for a few minutes longer. J. B. S. H. generally awoke from what appeared to him to have been a sleep, with dreams which he sometimes remembered. On one occasion he made swimming movements during recovery. The experience was in no way unpleasant. Subjects generally continued working at their assigned tasks until they lost consciousness. One subject, H. Ks., however, retched considerably and groaned while losing consciousness.

Our usual procedure was to raise the partial pressure of CO_2 by steps,

beginning with a partial pressure of about 4%, which all subjects tolerated, or of 6–8%, which some subjects tolerated. On raising the pressure, consciousness was generally lost in 1–4 min.

Table 1 shows the results as regards loss of consciousness in different subjects. L. J. appears to be the most resistant individual. He had previously had 8 min. at 3·8% and 5 min. at 6·9%. In 9·8% he was not only talking rationally, but his handwriting had barely deteriorated, and his notes were entirely sensible.

It will be seen that different people lose consciousness at very different partial pressures. Probably with short exposures of this type about half a group of healthy men and women would lose consciousness at 10 atm. in 0·8% of CO_2 within 4 min. But occasional individuals would be made unconscious by a partial pressure of 6%, and a very few might survive 10%.

Table 1

Subject	Partial pressure at which conscious	Partial pressure at which unconscious	Time in minutes at highest partial pressure
L. J.	9·8	—	1
J. L.	6·8	—	3
J. N.	6·7	—	3
E. M. C.	8·1	9·7	1
H. S.	8·1*	9·7	1
J. E. J.	8·4	9·2*	4
H. Ks.	6·8	9·2	1
J. B. S. H.	7·1	8·0	1
J. M.	4·3	7·3	2
O. D.	3·7	6·8*	5
J. P.	3·6	6·6	5

* Consciousness barely lost.

It must be emphasized that this table refers to rather short exposures, this being the most interesting question for certain practical purposes. Only two experiments were done involving longer exposures. J. B. S. H. and E. M. C. were exposed to an atmosphere whose CO_2 content rose from 6·00 to 6·35% at atmospheric pressure. After 19 min. both had slight headaches, as well as hyperpnoea. E. M. C. then put on his respirator. After 21 min. the pressure was raised to 10 atm.; the partial pressure was unaltered, save for a slight rise due to respiration. After 24 min. the maximum pressure was reached, and after 32 min. J. B. S. H. was unable to take rational notes, but was rational enough to ask E. M. C.'s permission to signal for decompression, and to give the correct signal. He would probably have lost consciousness very soon. The maximum partial pressure of CO_2 was 6·5%.

In a similar experiment H. Ks. was exposed to 6·0–6·4% of CO_2 at 1 atm. for 26 min. From 30 min. onwards he was at 10 atm. pressure. After 36 min. he could not write, and began to groan loudly and retch. After 37 min. he was unconscious, but recovered at once during the first decompression. The maximum pressure was 6·8%. Thus it is probable that most people would be unable to support partial pressures of 6% of CO_2 at 10 atm. for so long as

an hour, and we consider that, since even at 4% there was definite deterioration in manual skill after a few minutes, the partial pressure of CO_2 at 10 atm. should be kept below 3%.

The psychological effects noted under these conditions are interesting. They are well illustrated by the notes taken by H. S. during an experiment. The events are recorded in square brackets.

[11.41. Atmospheric pressure. CO_2 raised to 3·6%.]

'11.41. CO_2 let in. Sharp smell which persists. haven't noticed it before.'

[11.42. Compressed air let in.]

'11.44. Roaring in ear as in fainting begins. 11.45. Have become concicous of my change of conciouscouse. 11.46.'

[11.46. Maximum pressure reached. Hyperpnoea obvious in both subjects. 11.48. E. M. C. puts on respirator and raises CO_2 to 6·4%.]

'11.48–49. 2nd cylinder of CO_2. a few drops froze. I am still sweating but do not feel hot. Chase fanning makes me feel hyteropherateraperea.[1] 11.48. A length of word. —— then its all over.'

[The last line was actually written at 11.52. 11.52. H. S. seems fairly good. Thinks she could do a 'ball game' if called upon. 11.53. Third cylinder of CO_2 partly emptied. H. S. has glazed look, but continues writing.]

'2nd cylingder—but I have fainted all ready.'

[11.54. H. S. looks fairly bad. Trying to write. 11.55. CO_2 8·1%. H. S. cannot fan air, but has a determined expression and is moving lips, though not talking. 11.55. H. S. unmistakably unconscious. 11.56. E. M. C. removes respirator. 11.57. H. S. twitching and blinking. E. M. C. lifts her left eyelid, and looks at her pupil. This rouses her.]

'11.259. Chase has looked at my eye under my lid to eye If they have looked if I am still still...(illegible)...still conciocous.'

[11.58½. E. M. C. lets out remainder of CO_2 from third cylinder. This is his last recollection till decompressed. 11.59. E. M. C. takes sample (9·7% CO_2). 12.0. H. S. twitching. Both look 'dopey'. 12.01. Decompression begins. 12.01½. E. M. C. writes 'Woke up from what? heard decompression in progress'.]

'12.11. We have reduced the pressure. I dont know whether I ever lost conciousness. 12.3. The last time is wrong.'

[12.5. CO_2 1·00% at 100 ft. pressure. E. M. C. at first tried to take it in tube used for last sample, which he did not remember taking.]

'12.5. I may be sick. 12.7. The headache is developing. 12.9. I am afraid of thinking about being sick. 12.9½. Feel much better. 12.14. O_2 apparatus. I am concious of gaps of time, e.g. 9·5–14. 12.17. 12.21. I think all my senses are normal, but still an effort to write. 12.22. Still a tendency to tremble. 12.24. Hear the talking outside for the first time. 12.33. 12.44. Gradually waking up.'

[1] This word was intended to be 'hypertrophied', and to mean that the effect of fanning was exaggerated by the high air density.

[12.45. E. M. C. notes 'Still very blurred mentally. Cannot remember what decompression time ought to be for 16 mins. for example.' 12.59. Emerge from chamber.]

The handwriting gradually deteriorated, and finally became very illegible, but was almost normal by 12.5 p.m. The tendency to perseveration is notable. Thus on one occasion J. B. S. H. noted 'J. B. S. H. frequently coughs because of coughing due to ? NaOH in lungs'. At the end of 32 min. in 6–6·5% CO_2, the last 8 min. being at 10 atm., J. B. S. H. tried to read the dry and wet bulb thermometers, said there was something wrong with them, and wrote down '12·08° F., 1208° F., 1288° F.' (the time being 12.8 p.m.). On another occasion E. M. C., while losing consciousness, remembers saying, 'This is eternity; everything is just the same, for ever, and ever, and ever, and ever...' and then 'hyperpnoea, hyperpnoea, hyperpnoea...'. He noticed this tendency, but was unable to control it.

However, this perseveration was only noticed in some subjects. In others the most notable psychological symptom was elation. Thus J. E. J. whilst the partial pressure of CO_2, at 10 atm., was being raised from 6·5 to 8·4% wrote, 'I feel extremely cheerful and don't mind it a bit.' 2½ min. after the CO_2 had been further raised to 9·2%, she stated when questioned, 'I feel quite O.K.' When asked to write this down, she got as far as 'I feel', but this was followed by a meaningless series of pencil strokes. She shouted 'I will write it' so loud as to be heard outside the chamber, but then began swaying from side to side and had to be supported. She probably lapsed from consciousness, and certainly did not remember what had happened; however, she stated that it had not been unpleasant.

Both the Irish subjects were elated, and laughed vigorously from time to time. One of them swore a good deal during the skill test, and was first bewildered and then amused when told that he must use one hand only (he had performed it with one hand 12 min. earlier). This subject also believed that, during the first decompression, E. M. C. took a spanner out of his hands, and said there was to be no violence. As E. M. C. has no recollection of this, and had not lost consciousness, this was probably a dream.

Other subjects were very depressed. On compression to 10 atm. at a partial pressure of 4% CO_2, one subject seized E. M. C.'s hands and said, 'I'm going to die, I'm going to die, I tell you'. On being presented with the manual dexterity test, he said, 'No, I can't possibly do anything'. However, he was reassured, and performed the test fairly satisfactorily. Another subject showed almost equal alarm.

Subjectively E. M. C., before losing consciousness, passes through a stage where it appears to him that he has always been in the chamber, and always will be, whereas J. B. S. H. sinks gradually into more or less coherent dreams. Others are unaware that they have been unconscious. Others again have gaps in their memory during which they seemed to observers to be conscious. The sense of time may be disturbed. To J. B. S. H. time seems to pass quickly.

Similarly H. Ks., who took 28 sec. to make 30 taps (which he judged to be at intervals of a second) under normal conditions, and 32 sec. when breathing 6·4% of CO_2 at atmospheric pressure, took 60 sec. when the total pressure was raised to 10 atm.

There was often a slight headache during decompression, as is usual when the partial pressure of CO_2 is reduced at atmospheric pressure, but no subjects vomited at this stage. One (O. D.) noticed a smell of ammonia during decompression, as described by Haldane (1924) when first breathing normal air after exposure to CO_2.

COMBINED EFFECTS OF COLD AND PRESSURE

E. M. C. and J. B. S. H. lay inside the pressure chamber in a bath containing water and large amounts of broken ice. Ice was also piled as far as possible on the knees and other parts of the body emerging from the water. J. B. S. H. wore a shirt and trousers. He was comfortable for 12 min., the mouth temperature rising from 98·2 to 99·0° F., as is usual in his case. After 20 min. the teeth began to chatter, and the mouth temperature after 22 min. had fallen back to 98·3° F. After 23½ min. shivering was fairly violent, and the pressure was raised. 250 ft. was reached after 26 min. He felt much better than at the same pressure with 4% CO_2, and was able, when asked, to recite the words of a fairly lengthy song with few mistakes. The water temperature at the end was 33° F.

In a similar experiment E. M. C. wore a sweater instead of a shirt. After 12 min. he was shivering definitely, the mouth temperature remaining steady at 98·6° F. After 15½ min. he was feeling very uncomfortable, and was compressed to 300 ft. pressure, which was reached after 19 min. in the bath. He felt somewhat more comfortable. After 26 min. in the bath and 7 min. under pressure he was able to multiply 17×13 and 47×13 correctly in his head, whilst J. B. S. H., who had propounded the questions, and was taking notes, gave an incorrect answer to the latter. His mouth temperature was 98·4° F. He was decompressed during the 28th minute. Subjectively he felt 'perhaps somewhat more stupefied than he usually does at 300 ft.' during the third to fifth minute under pressure, but this passed off.

Both subjects noticed great hyperpnoea whilst breathing O_2 during decompression, after leaving the water. The shivering was sometimes so intense as to suggest clonic spasms. The O_2 consumption almost reached the maximum of 2 l. per min. permitted by the 'Salvus' apparatus, and the soda-lime canister became very hot.

It may be concluded that cold has a very slight effect, at most, in increasing the effects of N_2 narcosis. The difference between the two subjects was probably largely due to J. B. S. H. being fatter. However, it should be noted that E. M. C. is more tolerant of cold than most people.

Combined effects of carbon dioxide and cold

When standing in a tank of water at 39° F., with much ice floating in it, immersed up to the neck, and wearing a shirt, trousers, sweater, and pants, J. B. S. H.'s teeth began to chatter after 18 min., and shivering began after 20 min., the mouth temperature being 97·3° F. He emerged after 25 min. 11 min. after emergence the mouth temperature was 98·0° F., and 23 min. after emergence the rectal temperature (normally about 99·0° F.) was 97·5° F.

After breathing air containing 5·8–6·0% CO_2 for 2 min., the same subject entered the tank, the water temperature being 38° F. The teeth began to chatter whilst taking a mouth temperature after 21 min. Chattering was in general prevented by a rubber mouthpiece. Shivering began after 26 min. He emerged after 28 min. The mouth temperature had fallen to about 93·5° F., but this was probably from breathing cold air through a mouthpiece, the tube to which was partly immersed in melting ice. The rectal temperature 4 min. after emergence was 97·2° F. There was no headache, and shivering was about as intense as in the other experiment and in comparable ones. The experiment was rather less unpleasant than usual, perhaps through a narcotic effect of the CO_2.

It had been suspected that the CO_2 might cause vasodilation, and thus lead to a much greater effect of cold. On the contrary, the skin, which normally becomes very red in cold water, was less red than usual when CO_2 was breathed. It is clear that, in this subject at least, the effects of CO_2 and cold are not cumulative, like those of CO_2 and N_2.

Combined effects of pressure, carbon dioxide and cold

J. B. S. H. immersed himself in a bath of ice in the chamber as before. The partial pressure of CO_2 was raised to 6·5%. After 17 min. the teeth were chattering and the mouth temperature was 96·7° F. The subject was not uncomfortable. The CO_2 had fallen to 6·2%, through absorption by E. M. C.'s respirator. After 19 min. shivering began, and after 20½ min. the pressure was raised, 300 ft. being reached after 24 min. J. B. S. H. coughed violently.

After 2 min. at 10 atm. his attempts to recite the same verses as before gave rise to 'short disconnected bursts of words actually occurring in the work, but in disarranged order'. After 3 min. he was making rhythmical jerking motions of the limbs, quite distinct from shivering, and after 3½ min. was quite unconscious and irresponsive. The partial pressure of CO_2 was 6·9%, having risen because E. M. C. removed his respirator.

After 4½ min. at 300 ft. the pressure was lowered to 100 ft., and consciousness was partly recovered. After 31 min., whilst getting out of the bath, the mouth temperature was 95·2° F., and 5 min. later 94·5° F. During this decompression normal consciousness was only gradually re-established, J. B. S. H.'s first impression being that the chamber was a long and com-

paratively spacious tunnel. Whereas on three other occasions when this subject ost consciousness from the effects of CO_2 and pressure, recovery was always pretty rapid.

It may be concluded that cold somewhat enhances the combined effects of CO_2 and pressure, but it must be realized that the degree of cold was rather extreme. It is doubtful whether moderate cold would have a marked effect.

DISCUSSION

These experiments were conducted with certain practical ends in view, and we realize that they are in many ways incomplete. However, it is clear that air has a somewhat intoxicating effect at 10 atm., whilst a mixture of He or H_2 and O_2 has not. On the other hand, this effect does not get worse after the first 3 min. The further effect of CO_2 is not very great if this is calculated in terms of partial pressure. Thus, if a man were confined in an unventilated diving bell at 10 atm. he would not lose consciousness till the partial pressure of CO_2 rose to about 6%, as compared with about 10% at atmospheric pressure. As the rate of rise of partial pressure for a given metabolism is independent of the total pressure, this means that men could last for more than half as long at 10 atm. as at 1 atm.

On the other hand, if air containing 0·7% of CO_2, which has a quite negligible physiological effect at 1 atm., is compressed to 10 atm., almost everyone would be seriously affected, and probably unconscious after half an hour, whilst some people would lose consciousness at once. As against this, high partial pressures of CO_2 do not appreciably, if at all, increase the risk of symptoms arising from decompression. And it seems probable that no greater precautions against cold are needed at such high pressures than would be reasonable at ordinary pressures. All apparatus for respiration intended for use at high pressure should be tested for resistance at such pressures.

The physiology of N_2 intoxication presents some curious features. The rapidity of the onset and disappearance of the symptoms are remarkable. They are at their maximum after 2–3 min., and disappear in about the same time. On the other hand, Behnke, *et al.* (1935) find that the half-period of saturation of the body water and 16% of the lipoids with N_2 is about 7 min., that of the remaining 83% of lipoids being about 80 min. It follows that the part of the nervous system where N_2 produces its intoxicating effect must be a very vascular part, presumably the grey matter of the cortex. Thus the effects of high-pressure N_2 on the nervous system fall into two categories. The grey matter, or some of it, is rapidly saturated and desaturated. Hence the symptoms here described begin and end rapidly. But because of this rapidity of desaturation, decompression rarely causes mental symptoms, though maniacal attacks have been recorded. On the other hand, the white matter has a poor blood supply, and saturates and desaturates slowly. There is no evidence that dissolved N_2 impairs its activity in any way, though of course an exposure over many hours might have some effect. But this very slowness

of gas exchange leads to bubble formation during decompression, which gives rise to paralysis, and probably to pain also. We have no explanation to offer as to why CO_2 excess and N_2 excess appear to co-operate, whilst O_2 shortage and N_2 excess do not do so to any appreciable extent. The solution of such questions waits for two things: first, a general survey of the effects of so-called indifferent gases, including the inert gases and methane; and secondly, an attempt to determine which of the biochemical processes in the brain are interfered with by N_2 under high pressure. We hope to deal, in a later paper, with the effects of O_2 at high pressure.

SUMMARY

We confirm the finding of Behnke, *et al.* (1935) that air at 8·6 atm. pressure has a somewhat intoxicating effect on human beings, and that this effect is due to nitrogen. The nitrogen effect reaches its maximum after about 3 min. There was no reduction of manual dexterity in the test used by us, but a considerable effect on performance of arithmetic, and on most practical activities. At 10 atm. these effects were somewhat enhanced, and manual dexterity was lowered in some cases. When helium or hydrogen was substituted for nitrogen there was no intoxication.

3–4% of carbon dioxide at atmospheric pressure caused no deterioration in manual or arithmetical skill, and in the two subjects tested, 6% of carbon dioxide caused no deterioration.

When air containing about 0·4% of carbon dioxide, and therefore with a partial pressure of about 4%, was breathed at 10 atm., there was a marked deterioration in manual dexterity, and a good deal of confusion. When breathing carbon dioxide at partial pressures of 6·6–9·7% at 10 atm., eight subjects lost consciousness in 1–5 min., but some could tolerate partial pressures of over 8% for 5 min. or more. With half an hour's exposure to a partial pressure of 6–7% of carbon dioxide, one subject lost consciousness after 7 min. at 10 atm. pressure, and another nearly did so.

We consider that the percentage of carbon dioxide in air at 10 atm. pressure should be kept below 0·3%. Exposure to high partial pressures of carbon dioxide at 10 atm. does not increase the liability to 'bends' or other symptoms due to rapid decompression.

Immersion in water below 40° F. did not enhance the effects of high-pressure air, or of carbon dioxide at atmospheric pressure, but somewhat enhanced those of high pressure and carbon dioxide together.

In certain breathing apparatus the resistance became so great at 10 atm. as to be intolerable.

Few subjects experienced serious trouble during compression, or during or after decompression. But one developed a unilateral pneumothorax.

We have to thank Messrs Siebe Gorman and Co., who put their equipment and skilled personnel at our disposal, the Admiralty, who paid a salary to

one of us, and met a number of expenses, and Sir Leonard Hill, F.R.S., who watched many of the experiments and gave valuable advice. In particular we must thank those who volunteered for this work, and especially those who took part in repeated experiments, in spite of considerable discomfort in the earlier ones.

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(*MS. received for publication* 23. VII. 41.—Ed.)

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Report on Project Hydrox II		5. TYPE OF REPORT & PERIOD COVERED Final Report to Dec. 31, 73 6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Peter O. Edel		8. CONTRACT OR GRANT NUMBER(s) N00014-73-C-0233
9. PERFORMING ORGANIZATION NAME AND ADDRESS Michel Lecler, Inc. Harvey, Louisiana		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS Director Physiology Programs Office of Naval Research, 800 Quincy St. Arlington, Virginia 22217		12. REPORT DATE August 15, 1974 13. NUMBER OF PAGES
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)		15. SECURITY CLASS. (of this report) Unclassified 15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Hydrogen-Oxygen, Helium-Oxygen, Nitrogen-Oxygen, Breathing Mixtures, Decompression, Diving, Hyperbaric, Pulmonary Functions, Vital Capacity, Doppler Flowmeter, Bubble Formation.

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Since the world's supply of helium resources is diminishing, future deep diving operations may depend on substitutes for helium in breathing mixtures. On the basis of its physical constants, hydrogen would seem to be the most promising replacement for helium as an oxygen diluent in breathing mixtures for human exposure to very high pressures.

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S/N 0102-014-6601 |

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

Continued from Block 20

The experimental program involved four volunteer diver-subjects, each of whom was exposed on two separate occasions to 7.06 Absolute Atmosphere (ATA) for a period of 113 minutes while breathing a mixture of 97%H_2-3%O_2 for a total number of 24 dives. Each subject was exposed to each breathing mixture twice during the program. During the exposures, a work load was performed by the subjects and performance measurements were made. In addition, blood and urine samples were collected, a mass spectrograph analysis was made of the divers' inspired and expired breath, speech studies were conducted, pulmonary function measurements were made, and a doppler flowmeter was used to monitor the presence of bubble formation in the divers' blood stream during decompression.

The subjects' responses to decompression profiles for the three oxygen diluents were evaluated to provide provisional values with regard to hydrogen concerning uptake and elimination time for gas transport in the human body.

REPORT ON PROJECT HYDROX II

by

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This research was supported by Office of Naval Research
Contract N00014-73-C-0233 with funds provided by the
Naval Bureau of Medicine and Surgery and the
Office of Naval Research

August 15, 1974

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ACKNOWLEDGMENTS

The author wishes to express his gratitude to Dr. E. F. Coil of the Naval Hospital at the National Naval Medical Center, Bethesda, Maryland, for the scientific advice he rendered so generously.

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Peter O. Edel

ABSTRACT

Since the world's supply of helium resources is diminishing future deep diving operations may depend on substitutes for helium in breathing mixtures. On the basis of its physical constants, hydrogen would seem to be the most promising replacement for helium as an oxygen dilutant in breathing mixtures for human exposure to very high pressures.

The experimental program involved four volunteer diver-subjects each of whom was exposed, on two separate occasions, to breathing mixtures of 97%H_2-3%O_2, 97%He-3%O_2 and 97%N_2-3%O_2 at 7.06 atmospheres absolute (ATA) during an exposure period of 113 minutes for a total of 24 dives. Each subject was exposed to each breathing mixture twice during the program. During the exposures, a work load was performed by the subjects and performance measurements were made. In addition, blood and urine samples were collected, a mass spectrograph analysis was made of the divers' inspired and expired breath, speech studies were conducted, pulmonary function measurements were made, and a doppler flowmeter was used to monitor the presence of bubble formation in the divers' blood stream during decompression.

The subjects' responses to decompression profiles for the three oxygen dilutants were evaluated to provide provisional values with regard to hydrogen concerning uptake and elimination time for gas transport in the human body.

INTRODUCTION

A historical review of man's direct exposure to the environment in the exploration and exploitation of the hydrosphere clearly reveals the importance to future operations of developing optimum breathing mixtures for the specific conditions of the planned exposure. Any mixture selected will impose an ultimate limitation upon the user as to depth and operating proficiency

in the performance of assigned tasks. In order to translate the ultimate physiological limitations into practical operational procedures we must obtain precise knowledge of the manner in which a given breathing mixture affects the human body, which will then dictate the equipment and procedures required to achieve designated goals in diving operations.

Two fundamental problems have appeared in previous usage of various breathing mixtures. The first of these is intolerance to inert gases. The problems of narcosis with regard to nitrogen is well documented. It has been shown that the use of nitrogen-oxygen mixtures with current knowledge and techniques imposes a practical operating depth limitation of 7 ATA for most purposes. The practical depth limitation with helium-oxygen mixtures is not known at present, but recent human experiments at very high pressures indicate that the limits with this mixture may be rapidly approaching. Predictions based upon previous experiments with hydrogen-oxygen indicate that the use of this mixture may extend this ultimate depth limitation.

The second of these critical problems is the projected scarcity of helium. Recent predictions based upon reports of the Bureau of Mines concerning the available supply of helium and the projected consumption of this gas show that continuation of present trends will result in a depletion of our helium supply by the year 2000.[1] These figures suggest the advisability of exploring possible substitutes for helium wherever possible. Hydrogen appears to be a prime candidate as a substitute for helium in deep diving operations, considering previous data from manned and animal experimentation with this mixture. Furthermore, a source of the component parts of a hydrogen-oxygen breathing mixture exists wherever diving operations are undertaken--the water itself. Utilization of this infinite supply to produce the breathing mixtures on board ship as needed, would permit more favorable logistics with respect to gas supplies and greater flexibility of operation.

PURPOSE

A previous experimental series by Edel et al (1972) involving men and animals showed that diving operations with hydrogen-oxygen mixtures are feasible and that there are no obvious medical constraints to the use of this mixture within the limitations of the above exposure series.[2] However, further data would be

required to provide an assessment of the potential role of hydrogen-oxygen mixtures for future deep diving operations. It was the purpose of PROJECT HYDROX II to generate such data by a comparative study of decompression response, pulmonary functions, speech patterns, behavioral scientific observations of performance, and the use of a doppler system for the detection of bubbles in the blood stream. During a portion of the experimental series, personnel and equipment of the Naval Submarine Medical Research Laboratory were involved. Michel Lecler, Inc. was responsible to the Office of Naval Research and the Bureau of Medicine and Surgery for the overall operation of the program, including supervising personnel safety, providing the decompression schedules required, providing personnel to perform as test subjects, operation of the hyperbaric chamber (including the selection and supply of the necessary gas mixtures for breathing and operational performance of the chamber) providing assistance as required to the Navy team, and studying comparative decompression responses from these exposures. The Naval Submarine Medical Research Laboratory participation involved conducting comparative studies of pulmonary functions and speech patterns, biochemical estimates, behavioral scientific observations of performance, the use of the doppler flowmeter for the detection of bubbles in the blood stream, the use of a mass spectrometer for a continuous analysis of expired gases, and providing the necessary equipment and personnel to carry out these assigned tasks.

In addition to the hydrogen-oxygen dives, identical exposures were also made using helium-oxygen and nitrogen-oxygen (as the two best known diving gases in terms of available physiological data) to provide a basis of comparison for measurements conducted under identical conditions; the subject population was exposed to all three breathing mixtures during the course of this program. It was the purpose of the experimental design to provide a basis for the evaluation of hydrogen in comparison with helium and nitrogen with respect to the above mentioned studies at a pressure of 7.06 ATA during the two hour exposure period at that pressure. More importantly, this data was generated in order to examine hydrogen-oxygen as a possible substitute for other mixtures currently in use for under-water diving operations.

BACKGROUND

In the history of manned diving operations, man's principal effort has been to overcome the biological problems affecting him at raised environmental pressures. These problems may be

divided into numerous categories, yet almost any physiological problem at increased pressure will be effected by one common denominator--the breathing mixture used. Not until the breathing mixture has been chosen for a specific operational procedure at a given depth can the magnitude of virtually all the physiological interactions be expressed within the accuracy of our present knowledge. Our prime concern today, as in the past, must therefore be the choice of the breathing mixture required for the specific manned diving operation and the resulting physiological limitations which will be imposed by such a choice.

Normally the more complex solution to a given problem is the result of failure (or presumed failure) of a simpler solution to fulfill the requirements of a specified task. This, of course, presupposes that man will initially attempt to utilize the simplest known solution to solve his problem. A review of the history of diving shows this assumption to be valid in this case. Since man has been surrounded by a sea of air since his evolution as a species upon this planet, it was only natural in his first attempt to exist below the surface of the water with an externally supplied breathing mixture to choose air as the breathing medium for such an excursion. Since the pressures involved in man's initial dives were not greatly in excess of one atmosphere, and the duration of his exposures were extremely short by today's standards, it is not surprising that air served admirably for the needs of that time.

However, upon deeper and more extended excursions, it became evident that thought processes were effected at depth. In 1878, Paul Bert ascribed narcotic properties to air breathed under sufficient pressure.[3] Further dives to depths beyond 150 feet added to the data describing the effect of what later became known as nitrogen narcosis, confirmed the observed effect of such narcotic properties, and indicated the existence of a depth limitation with respect to air breathing mixtures. Difficulties in producing pressure reduction schedules with air as the breathing medium which would adequately comply with human decompression requirements even below pressures which produce readily observable narcosis led investigators Sayers, Yant and Hildebrand in 1925, to suggest the substitution of helium-oxygen mixtures in place of air as a means of preventing decompression sickness.[4] Although in animal experiments they had found a reduction of decompression time of 6:1, later experiments by Momsen in 1939 involving nearly 700 simulated dives with humans in depths up to 500 FSW (Feet Sea Water) showed no advantage in decompression following helium-oxygen exposures as compared with previous experience using air.[5] Perhaps a more meaningful finding in terms of modern diving resulting from those experiments was the noted absence of

narcosis at such pressures with helium-oxygen, confirming the work of Behnke, Thomson and Motley in 1935 suggesting nitrogen as the responsible factor for the narcosis.[6]

Over the last 30 years helium-oxygen has been utilized as a breathing mixture in depths far beyond the practical operational limits of air diving. In 1965 came the first hint that there might be a pressure limitation for this mixture resulting from exposures with helium-oxygen in simulated dives to pressures between 10 ATA (300 FSW) and 25 ATA (800 FSW).[7,8,9] In these manned experiments, marked impairment of performance occurred, accompanied by nausea and severe tremor (helium tremors) of the hands and body. The impairment tremors were quite severe at 800 FSW with a 95%He-5%O_2 breathing mixture following a descent rate of 50-100 FSW per minute. These results contrasted with experiments reported by Cabarrou in 1966, who noted the absence of such symptoms during a 100 hour exposure at 25 ATA (800 FSW) with a mixture of 1.5%O_2-3.5%N_2-95%He, following an average descent rate of 13 FSW/min.[10]

It has been shown by Brauer, Way and Perry in 1967 that the onset of the "helium tremors," or HPNS (High Pressure Nervous Syndrome) as it is now called, could be postponed to higher pressures by the addition of nitrogen to the helium-oxygen mixture.[11] Further, it has been demonstrated by The Royal Navy in 1971[12] and Fructus in 1971[13] that pressure exposures in simulated dives are possible to 1510 and 1705 FSW respectively by reduction of the rate of pressurization using a mixture of helium-oxygen. However, at least in the dive to 1510 FSW, some degree of impairment from HPNS was noted, and both exposures showed some EEG changes. Comparison of effects observed during such simulated dives suggests that the practical operational depth limit for working dives is being rapidly approached, or may even have been exceeded in such experiments using helium-oxygen mixtures.

It is apparent that for dives considerably in excess of the maximum depth penetrations (approximately 2000 FSW, achieved according to Fructus in 1972)[14] and possibly even at shallower levels, a more appropriate mixture is required. Ideally, such a mixture must contain the following properties:

1. It must be essentially "biologically inert."

2. It must permit a significant increase in operational depth range with a narcotic potency not to exceed the equivalent result from an exposure to 200 FSW with air, nor the equivalent impairment with respect to HPNS resulting from an exposure to 1500 FSW with helium-oxygen.

3. It must show favorable decompression characteristics as compared with helium-oxygen.

4. Its respiratory limitations must be comparable or superior to helium-oxygen.

5. It must have response patterns to treatment for decompression sickness which are comparable to or superior than those in which nitrogen or helium are involved.

6. It must be comparable or superior to helium-oxygen in terms of present-day cost and availability.

7. It must be reasonably safe for experimental use and for projected open-water operations.

A preliminary list of oxygen dilutants for comparison against the above list might include xenon, krypton, argon, helium-nitrogen mixtures, neon, and hydrogen. Initially we can rule out argon, since the work of Behnke & Yarbrough in 1939 has shown that argon has a greater narcotic potency than nitrogen.[15] Work done with xenon and krypton by Lawrence et al in 1946 has demonstrated that these inerts have greater narcotic potency than either nitrogen or argon, and therefore must also be deleted as possibilities.[16]

Neon was first utilized as a breathing mixture during portions of a 48 hour exposure at 650 FSW reported by Hamilton et al in 1966.[17] Both subjects in the experiment breathed a mixture of 90%Ne-10%O_2 for 30 minutes at 650 FSW. No symptoms of narcosis or HPNS were detected as a result of this breathing mixture. In later experiments conducted by Lambertsen et al in 1972, subjects were exposed to neon-oxygen mixtures at a simulated depth of 1,200 FSW in order to investigate the effects upon respiratory work and performance of men during acute exposure to breathing mixtures simulating the equivalent gas density which would result with a helium-oxygen breathing mixture at a depth of 5,000 FSW.[18] Although breathing neon-oxygen did not result in any problems at lower pressures, the condition of the two test subjects, after breathing this mixture while exercising at 1200 FSW, warranted a prompt return to a helium-oxygen mixture prior to the completion of the planned period of neon-oxygen breathing.[19] The maximum depth range with neon-oxygen mixtures for commercial diving operations was recommended as 700 FSW by Schreiner et al in 1972.[20] Neon-oxygen is therefore more restrictive with respect to pressure than helium-oxygen and should be removed for consideration, leaving nitrogen-helium-oxygen and hydrogen-oxygen mixtures as the remaining candidates.

To assess the ultimate depth potential of these remaining candidates is most difficult in view of the lack of relevant data. The above mentioned experiment showed that in terms of gas density, breathing helium-oxygen in acute exposures at some pressure between 3,000 and 5,000 FSW is feasible with above-average physical specimens. However, major questions still remain concerning the potential use of $He-O_2$ or $He-N_2-O_2$ mixtures for diving operations at 1,500 FSW or greater pressures.

One major question concerns HPNS. Since there is no data to suggest that the properties of neon are in any way comparable to helium in this respect, we must return to the data of The Royal Navy[12] and Fructus in 1971,[13] which show some undesirable effects under conditions less severe than would be anticipated under actual open-water operational conditions. Slow compression rates were required in these experiments (as has been previously mentioned), and it has been suggested by Brauer in 1967 that the addition of nitrogen to the mixture may confer additional depth advantage over the use of helium-oxygen alone.[11] However, this in turn would increase the breathing resistance which at depths below 1,500 FSW may already be in excess of desirable limits for working divers in practical open-sea operations.

The 1,600 FSW simulated dive conducted by the U.S.N. Experimental Diving Unit showed a marked inability of the subjects to do moderate or heavy work in immersed exercise studies with the MK10 MOD 4 underwater breathing apparatus and a remarkable loss in balancing ability at maximum depth.[21] This would suggest a maximum depth limitation for operational open-water dives of less than 1,600 FSW with helium-oxygen. Further complications resulting from high breathing resistance may be caused by problems in pulmonary diffusion of oxygen. While compressing goats breathing "normoxic" mixtures of helium-oxygen, Chouteau in 1967 and his associates observed what they referred to as a hypoxic crisis in the animals at a pressure of 50 ATA (approximately 1,617 FSW), which was relieved by increasing the O_2 partial pressure in the chamber atmosphere.[22,23] As further pressure increases resulted in recurrence of the phenomena, Chouteau et al were able to relieve the symptoms associated with hypoxia by further increases in oxygen partial pressure.

This result coincides with Lanphier's 1967 prediction of the pressure at which diffusion deadspace might be expected to cause difficulty with pulmonary diffusion of oxygen with an $He-O_2$ mixture and a respiratory frequence of about 8 breaths per minute.[24] Although subsequent investigations of the Chouteau effect have been made by others, to date no one has actually duplicated the conditions of the experiments performed by Chouteau.

While depth increases beyond 50 ATA are possible by increasing oxygen partial pressure beyond normoxic levels and addition of nitrogen might modify the HPNS and $CNSO_2$ toxicity, thus allowing higher oxygen partial pressures to be utilized and/or deeper depths to be achieved with helium-nitrogen-oxygen mixtures, a point is reached wherein pulmonary oxygen toxicity intervenes to limit further depth increases. Further the increased gas density which would result from addition of oxygen and/or nitrogen would be expected to reduce the practile open water operational limits due to ventilatory limitations imposed by existing underwater breathing apparatus.

We must then examine hydrogen with regard to our predetermined requirements as the remaining candidate for the ultimate depth attainable by man with gas breathing mixtures. Unfortunately, hydrogen-oxygen mixtures have excited little interest until recently.

In addition to Lazarev (1941)[25] who exposed animals to a hydrogen-air mixture under pressure, Zaltsman (1961)[26] reported some experiments conducted by I. I. Savichev involving compression of white mice to 90 ATA on a hydrogen-oxygen breathing mixture. Symptoms suggestive of HPNS were observed at 15-40 ATA and progressed during pressurization until, at pressures of 35-90 ATA, death occurred. This development contrasted with their results from helium-oxygen experiments in which death occurred at pressures of 65-120 ATA. This would seem to discourage potential use of H_2-O_2 mixtures if it were not for the fact that, at least in the one case cited, the compression from 0 to 90 ATA was accomplished within 30 minutes.

Further discouragement to the possible use of hydrogen-oxygen as a potential breathing mixture for deep diving operations resulted from the findings of Michaud et al in 1969, who found that the EEG of rabbits exposed to a pressure of approximately 30 ATA breathing hydrogen-oxygen gradually diminished in amplitude until death occurred within 15 to 45 hours.[27] This is in apparent contradiction to Brauer's (1967) experiments in which he succeeded in exposing a Rhesus monkey to a hydrogen-oxygen breathing mixture at a simulated depth of 1,551 FSW.[28]

Human experimentation with hydrogen-oxygen, although very limited in scope, has indicated no problems resulting from this breathing mixture. The earliest such experiment on record was carried out by Case and Haldane in 1941; a hydrogen-nitrogen-oxygen mixture was breathed for approximately 5 minutes at 10 ATA, and no adverse effects were noted.[29] Shortly thereafter, Zetterstrom in 1948 produced hydrogen-nitrogen-oxygen by cracking NH_3, to which, after scrubbing, he added oxygen to obtain a mixture of $72\%H_2$-$24\%N_2$-$4\%O_2$.[30] This mixture was used to make open-sea dives to 40 and 110 meters.

In addition, two dives were made to 70 and 160 meters using a mixture of 96%H_2-4%O_2, (Bjurstedt and Severin (1948)).[31] The final dive to 160 meters resulting in the untimely death of Arne Zetterstrom was due to mechanical failure and was in no way connected with the breathing mixture utilized in this experiment. Unfortunately, his tragic death discouraged other investigators until recently from continuing this work with human subjects.

A more serious and realistic drawback to such investigations was the commercial scarcity of hydrogen-oxygen mixtures and the difficulty in mixing these gases, since within certain limits, these mixtures may be flammable and even explosive. Studies to determine the flammable limits of hydrogen-oxygen mixtures by Coward and Jones (1952)[32] and Dorr and Schreiner (1969)[33] have demonstrated that the Zetterstrom mixture of 96%H_2-4%O_2 is neither flammable nor explosive. A study by the Royal Swedish Navy (1967) has shown that the explosive limits are well above the previously established flammability limits in the range tested (1-200 ATA).[34]

The development of a safe and reliable procedure by Edel (1972) for mixing hydrogen and oxygen in high pressure cylinders with up to 3% oxygen in hydrogen provided the availability of such mixtures for experimentation.[35] The mixtures were used by Edel (1969) to make two dry chamber dives to a simulated depth of 7.06 ATA for 10 and 20 minute exposure times.[36] One mild case of decompression sickness was encountered in the latter dive. Symptoms which occurred in the left elbow at the 40 FSW decompression stop underwent spontaneous remission at that level. Symptoms would then appear at each pressure change during decompression (which was continued unaltered, in accordance with the pre-planned schedule) and undergo spontaneous remission at each level up to and including arrival at surface pressure. These experiments demonstrated the feasibility of experimenting with hydrogen-oxygen mixtures and paved the way for an extension of the manned studies at 7.06 ATA by Edel et al.[2] These involved exposures with human subjects at 7.06 ATA of 20 minutes to 120 minutes (the latter including up to 108 minutes of hydrogen-oxygen breathing). The experimental series also involved two hydrogen-oxygen exposures with dogs, with the deepest animal test made to 1,000 FSW for a duration of 39 hours at that depth. Analysis of pre- and post-dive blood and urine samples failed to indicate any contraindication to the use of hydrogen-oxygen mixtures under the conditions tested.

The potential hazards involved in handling hydrogen-oxygen were investigated during this program, and the additional exposures confirmed the experimental safety of this mixture. It appears obvious that normal operational diving conditions in open water wherein the diver may exhaust his expired gas directly into the surrounding water (as opposed to dry chamber conditions requiring special exhaust systems) would result in increased operational

safety. In addition, communication studies were made by Sergeant (1972) which failed to indicate any significant increase in speech distortion with hydrogen-oxygen as compared with helium-oxygen breathing mixtures.[37]

RESEARCH GOALS

1. To obtain comparative decompression data with hydrogen, helium and nitrogen, from which the decompression obligation resulting from hydrogen-oxygen exposures can be assessed with relation to known requirements with helium-oxygen and nitrogen-oxygen.

2. To indicate through the above data the probable mechanism of gas transport in the slowest bodily tissue medium.

3. To obtain mass spectrometer data which will provide some indication of uptake and elimination times with hydrogen in the faster tissues by comparison with nitrogen and helium.

4. To obtain pulmonary function measurements to indicate probable maximum depth limits of hydrogen-oxygen as compared with helium-oxygen.

5. To obtain performance data which would indicate the relative performance decrement using hydrogen-oxygen breathing mixtures as compared with helium-oxygen and nitrogen-oxygen.

6. To obtain blood and urine samples to measure possible biochemical changes which might occur with hydrogen-oxygen mixtures, and hence indicate biomedical safety concerning hyperbaric exposures with this mixture.

7. To obtain speech recording with all three gases used as a breathing mixture to indicate the relative communication problems with hydrogen-oxygen breathing mixtures under pressure.

8. To monitor the divers via a doppler flowmeter during decompression to provide possible indications of subclinical bubble formation not resulting in obvious signs and symptoms of decompression sickness, and evaluate the use of the doppler flowmeter by correlating such measurements with the recorded occurrence of bends resulting from the use of the schedules involved in this program.

9. To obtain indications of potential operational difficulties pertaining to the handling of hydrogen-oxygen gas mixtures in practical operations by evaluating operational performance in handling such systems used in connection with this experiment.

10. To extrapolate all data gathered to provide any indication of potential depth limitations which could exist in the use of hydrogen-oxygen breathing mixtures.

METHOD

In PROJECT HYDROX II four (4) volunteer civilian divers were exposed to a pressure of 7.06 ATA (200 FSW) for 120 minutes (including descent time), using breathing mixtures of 97%H_2-3%O_2, 97%He-3%O_2, 97%N_2-3%O_2, in sequential dives. In the series of 24 manned exposures, each subject made two dives in the dry hyperbaric chamber with each of the three mixtures. All the experiments were conducted in a double-lock hyperbaric chamber 196 1/2" long and 49 1/2" in diameter which was especially modified for use with hydrogen-oxygen mixtures. The chamber was controlled from a central control panel designed for use with hydrogen-oxygen mixtures. Breathing mixtures other than hydrogen-oxygen were supplied to the diver by means of a demand mask from one of two chamber supply systems (main and auxiliary), each of which was connected to 5 cylinder lines, which were in turn connected to the cylinder manifolds. Crossover valves permitted the selection by means of selector valves from the central control board of any of the ten supply lines (in addition to 5 additional lines from a separate system connected to the outer lock) leading to either of the two main supply systems in the inner lock. Hydrogen-oxygen was delivered through a separate isolated system (without crossover valves connected to the outer lock or inner lock main and auxiliary systems) to the chamber connected to two banks of hydrogen-oxygen. The exhaust from the hydrogen-oxygen demand regulator masks was delivered to a 100 liter Douglas bag, which, during hydrogen-oxygen breathing periods, was maintained at the 50% level $\pm$ 20%. The breathing bag was exhausted through a flow control valve to a line terminating in a water-filled flashback arrestor outside the building.

Continuous monitoring of the chamber (inner lock) temperature, pressure, (PO_2, and PCO_2) took place throughout all dives in this experimental series. The chamber pressure was monitored by a Heise gauge having a certified accuracy of 0.1% of full scale with a range of 0-200 FSW. The accuracy of this gauge was checked with a deadweight tester within 30 days prior to the initial test in this series. This gauge was connected to a Heath-Schlumberger Eu-205B strip chart recorder to obtain a pressure-time record of all dives in this series.

Differential pressure measurements of all dives in this series were made using a Valdyne pressure transducer to indicate any deviation of pressure from the prescribed limits. This unit was calibrated against the Heise gauge at maximum pressure during each dive. Following the calibration, the scale was expanded to maximum sensitivity (full scale readout of $\pm$ 0.3 FSW from center pressure setting) to detect any small pressure deviation occurring within a given ten minute (or less) interval.

During the hydrogen-oxygen experiments the chamber pressure was controlled by maintaining the differential gauge readout "on scale" (± 0.3 FSW) by controlling the exhaust rate from the Douglas 100 liter volumetric bag into which the expired hydrogen-oxygen was exhausted from the diver's mask. During the period spent breathing the H_2-O_2 mixture, the bag level was periodically checked. Maintaining the system pressure in this manner was based upon the premise that gas expired into the Douglas bag should equal the exhaust from the bag, and therefore no change in bag volume would result. If the Douglas bag had been observed to decrease with time (while the pressure transducer was being maintained "on scale") this would indicate the exhaust out of the bag was greater than the exhaust into the bag, hence pointing to leakage of gas into the chamber. Such a leakage would have been assumed to be from the hydrogen-oxygen system and would have required the following steps in sequence:

1. Cutoff of the hydrogen-oxygen supply.

2. Switching the diver to the main or auxiliary breathing system (supplied at that time with 97%He-3%O_2).

3. Purge of the system with pure nitrogen.

4. Restoration of the chamber atmosphere to normoxic levels.

5. Abortion of the dive on the H_2-O_2 decompression schedule.

Chamber oxygen and CO_2 levels were monitored by a 1/8" O.D. (0.031" wall thickness) bleed-off line from the chamber which was connected to the analyzers by an air products flowmeter. A Beckman Model 888 polagraphic oxygen analyzer and a Beckman Model IR 415 A CO_2 analyzer were used for chamber atmosphere monitoring and were calibrated from calibration gas mixtures with certified accuracy before and after (and, when necessary, during) the dives. In accordance with manufacturer's recommendations, a flowmeter setting of 145 cc/min. ± 10 cc/min. was used. The outputs of both analyzers were connected to Heath-Schlumberger EU-205B strip chart recorders to maintain a continuous record of O_2 and CO_2 levels throughout the dives. Chamber temperature was monitored with a thermistor type thermometer. The thermistor itself, located in the chamber, was enclosed in a wire mesh flashback arrestor. The output of this instrument was connected to a Heath-Schlumberger recorder for a continuous record of temperature changes throughout the pressure profiles.

All breathing mixtures supplied to the chamber were within ± 0.5% of their indicated values except as noted: 65%N_2-35%O_2 mixtures were within ± 1% of the indicated value; 97%N_2-3%O_2, 97%He-3%O_2, and 97%H_2-3%O_2 mixtures contained an oxygen percentage not less than 0.1% lower, nor more than 0.2% higher than specified. The oxygen partial pressures in these gases at 7.06 ATA had a maximum range of between 0.205 and 0.225 ATA.

All test subjects were given a complete divers physical examination before being permitted to participate in this program.

Prior to the initial dive of the planned series, two manned exposures were made to check the operation of the doppler flowmeter in the hyperbaric chamber. The initial dive (originally developed for NASA by Edel (1970)[38] was made to a depth of 47 FSW for a duration of two hours. This profile was repeated three hours after completion of the initial dive, with a direct ascent to the surface following both exposures. See Figure 1. The second dive (originally developed for M & E Marine Diving Company) consisted of 5 minutes spent at 250 FSW with a multi-inert breathing mixture using the decompression profile shown in Table 1 and Figure 2.

Both profiles had previously undergone rigorous testing and had been found to produce incidences of bends in less than 1% in subjects chosen at random from the diving population. The low incidence of bends resulting from these profiles made them suitable for establishing the experimental safety with respect to the doppler flowmeter for planned use in the programmed series of 24 dives. This test was prompted by the assumption on the part of some investigators that the sonic signal generated by the unit in its normal operating position (in contact with the body by means of a gel transducer-tissue interface) could possibly cause sufficient cavitation in blood vessels in the immediate proximity to the transducer as to produce bubbles which would not normally have been formed during decompression had this device not been utilized.

During a portion of the test dive series, personnel from the Naval Submarine Medical Research Laboratory conducted tests on participating subjects involving performance measurements, biomedical observations, pulmonary functions, speech recording, and breath-by-breath analysis of gas exchange.

Performance measurements involved mental arithmetic, signal detection tests, sentence comprehension, and short-term memory.

Mental arithmetic test (MA). Two kinds of mental arithmetic problems often used in studies of the debilitating effects of unusual environments were presented. The addition-subtraction

task described by Adams (1958) required subtraction of a three digit number from the sum of two such numbers.[39] The multiplication task often used in British studies of diving, e.g., Rashbass (1955), requires multiplication of a two digit number by a one digit number.[40] Nine sets of 60 problems, 30 addition-subtractions followed by 30 multiplications, were formed by random selection from those defined by Adams and by Rashbass. For each subject the problems were projected onto the wall of the chamber at a rate found during training to produce an error rate of approximately one-third, 7-9 sec/problem for addition and 3-5 sec/problem for multiplication. Subjects were required to solve all problems column by column from right to left, recording solutions on a printed answer sheet.

Short term memory test (STM). The Paced Sequential Memory Task devised by Lloyd, Reid and Feallock (1960)[41] was used to assess the effects of the hyperbaric environments on short term memory. To control for differences in the auditory and speech environments presented by the several inert gases, the items were presented visually, by the projection on the chamber wall, rather than via the auditory channel employed by Lloyd et al and responses were written rather than spoken. The sequence consisted of two types of words interspersed: class names (e.g. tree, sport, city), which were shown on a colored background, and names of class members (e.g. maple, boxing, Paris), shown on a white background. The subject's task was to remember each item as presented until the name of its class appeared. Guessing was encouraged. There were eight classes of items and five items within each. By design, the maximum number of items to be held in memory was limited at any given time to five, and the mean active list length was three items. Each of the four test sequences employed consisted of the same 80 words, the 40 items and their corresponding 40 class names (hence 40 recall points), but in different orders. With one exception, the subject's rate of response was controlled by the five second duration of word presentation. After two near perfect performances, slide exposure time was reduced to four seconds. The subject recorded his responses serially on a printed answer sheet.

Signal detection task. This task simulates a visual display of sonar information (DIMUS) in which a target may appear against a "noise" background. The subject's tasks were to determine whether or not a target was present in an array of dots projected on the chamber wall and to assign a rating (1-4) to his confidence in the determination. In a non-target (noise) slide, on the average 24 dots are located at random in each column of the 60 column 48 row array; in a target slide, an average of 34 (70%) dots are located in a randomly

selected target column. The single set of 125 stimulus slides (63 targets) was presented in one of 120 random orders in each test session. To maintain comparability of the data from this study with that obtained previously (Ryack and Walters, 1972)[42] the events within a trial were: stimulus slide (3 sec.); blank slide during which presentation the subject was to mark the printed answer sheet (1.75 sec.); and feedback slide (1.25 sec.) which identified the stimulus as target (YES) or noise (NO). Feedback was provided to promote subject interest in an intrinsically difficult task.

Sentence comprehension test (SC). A short sentence comprehension test that has been used successfully by other investigators to evaluate nitrogen narcosis was used in these dives, Baddeley et al (1968),[43] Davis et al (1972).[44] Subjects were given booklets containing sentences such as, "A is followed by B. -- AB," or "B does not precede A. -- BA," and asked to judge whether the sentence was true or false with respect to the pair of letters that followed. Sentences contained all combinations of (a) "precede" or "follow." (b) affirmative or negative, (c) active or passive voice, (d) A or B as subject, and (e) AB or BA as the letter pair. These options define $2^5 = 32$ different sentences, and each was used twice to create booklets containing 64 sentences. Four different booklets exemplifying different random orders of the sentences were prepared. Subjects responded by circling a T or F in their booklets and had three minutes in which to do as many sentences as they could (see Table 2).

Training. For all tasks training was conducted over a period of several days immediately prior to the first 200 FSW exposure. Except for the signal detection and mental arithmetic tests, the bulk of the training was completed in four group sessions. In the first session for each subject printed instructions and sample problems from each task were reviewed; then one set of problems from each task was presented. Subsequent sessions differed only in the versions of the tasks presented, the number of subjects tested simultaneously, and, in the case of mental arithmetic, the time allowed for problem solution. Training on the signal detection task was terminated after each subject had completed six sessions. Each subject's training in mental arithmetic continued until rates of presentation were found which consistently produced 50-75% correct for him. Three subjects required 9 training sessions and one 16 sessions.

Test Procedures. The first tests on each diving day were administered in the open chamber at 1 ATA air (without masks) in the order MA-STM-SD-SC. The subject wore the demand mask during all subsequent tests. The MA test was administered at t+5 minutes of the exposure at 200 FSW, the STM and SD tests

were completed in sequence beginning at t+23, and the SC task was performed at t+101. During decompression, the STM test was presented as soon as possible after return to 60 FSW, and the SD and SC tasks were given at the 50 FSW stop. Gas mix at those stops was always 65%N_2-35%O_2. All four tests were administered in the standard order on stabilization on oxygen at 10 FSW. Subjects were not informed about their performances during the test dives. All four sequences of the STM and SC tests were presented to the subject during a dive with the order of the sequences counterbalanced over dives. The order of presentation of the nine sets of mental arithmetic problems was randomized over each block of three dives.

Biochemical Observations

To provide control data, urine was collected from each of the diving subjects in two 12 hour samples for at least 5 days before the dives. On the day of the dives, urine collections were made for the compression and pressure periods, the decompression period, and the remainder of the day. Sampling was continued according to schedule for the control days for four days following the dives. Blood samples were collected daily on the pre- and post-dive days. On the days of the various pressure exposures, samples were obtained before the dive, at the beginning of decompression and at the end of decompression.

Measurements were made of urinary volume, protein, osmolarity, calcium, sodium, potassium, ketosteroids, ketogenic steriods, urea nitrogen, creatinine, uric acid, phosphate and hydroxyproline. Serum and whole blood analyses were performed for clotting time, platelets, hemoglobin, hematocrit, red cell and white cell members, reticulocytes, differential leucocyte populations, fibrinogen, osomolarity, urea nitrogen and uric acid.

Mass Spectrometer Studies

Breath-by-breath analysis of gas exchange for 6 gases (oxygen, carbon dioxide, nitrogen, helium, hydrogen, and argon were monitored with a Scientific Research Instruments Medical Mass Spectrometer (Med-Spect. Model MS-8) during the periods of time when the subjects were exposed to pressure. The instrument was used in the respiratory mode, which has a response time of 60-70 miliseconds and draws about 100 cc/minute at the surface. The mass spectrometer was located outside the chamber; its inlet was a teflon-covered stainless-steel canula which passed through a penetration into the chamber. This canula had a quick disconnect fitting for a vinyl tubing nasal catheter (.928 inch I.D., .046 inch O.D.). The catheter was placed in the external nares and held on the face

with paper tape. It passed between the oral nasal mask and the face. The vinyl tube was changed fairly frequently, as it tended to become blocked with moisture and mucus. The steel canula had to be cleared with high pressure gas a few times during the series of dives.

The mass spectrometer was used in the summation mode, which reports the data in a unit that appears to be "mm Hg," though it is actually a fraction or percentage of the total the machine was initially set for. The following example will illustrate:

Room air or chamber air under pressure
Air under pressure
BP=760 mm
Subtract saturated water vapor at 37°C.
760-47=713 mm

Set total for 713 mm
O_2=20.93% X 713=149 mm
N_2=78.09 X 713 = 557 mm
Ar = 0.93% X 713 = 7 mm

Total (Summation) 713 mm

Different mixtures of 4-8% CO_2, 50% H_2, and 50% He were then used to set these gases. The total "mm" of all six gases in a sample in any combination will now total 713 "mm" regardless of the barometric or chamber pressure. Results from chamber use would have to be multiplied by the appropriate atmospheres absolute factor (e.g., 200 FSW = 7.06 ATA), etc. to give actual partial pressure in mm H_2.

The mass spec was connected to a Beckman-Type R Ink recorder, a Beckman-Ampex Model PR-55 tape recorder, and a Beckman Model EO-18 oscilloscope.

Breath-by-Breath Monitoring

Monitoring of six gases (O_2, N_2, CO_2, He, H_2, and Ar) was done throughout the respiratory cycle almost continuously throughout the ten hour dive studies. The only exceptions were during pulmonary function testing, part of the speech test, changing nasal catheter, recorder paper, recorder tape, and temporary breakdowns.

Pulmonary Function

Pulmonary function tests were done primarily to compare flow rates with these less dense mixtures of 3% oxygen in hydrogen, 3% oxygen in helium, and 3% oxygen in nitrogen used at 200 FSW

with flow rates of air. Although the 97%N_2-3%O_2 mixture is only slightly less dense than air, the 97%He-3%O_2 mixture is considerably lighter than the conventional He-O_2 mixtures used at this depth. The 97%H_2-3%O_2 mixture has only rarely been used by man as a breathing medium, and, prior to these tests, pulmonary function tests have never been performed with this mixture.

The six perimeters measured were as follows:

(1) Forced vital capacity (FVC) in liters.

(2) Forced expiratory volume in 1 second (FEV_1) in liters.

(3) Forced expiratory volume in 2 seconds (FEV_2) in liters.

(4) Maximum expiratory flow rate (MEFR) in liters/second.

(5) Maximum inspiratory flow rate (MIFR) in liters/second.

(6) Maximum voluntary ventilation (MVV) in liters/minute.

The first four values are obtained from one maneuver in which the subject inhales completely, followed by exhaling as rapidly and completely as possible. MIFR is obtained by a near maximum expiration, followed by as rapid an inhalation as possible. MVV is run at approximately 45-65% of FVC and as frequently as possible at this volume for 15 seconds. Each test was run twice and the higher of two valid-appearing results was used.

A Med-Science Electronics Model 370 wedge spirometer, Model 280 Pulmodigitizer, and a Model 281 MVV computer was used. A Tektronic Model 503 oscilloscope was used for monitoring of chest position and coaxing purposes. Only the wedge bellows unit was inside the chamber.

Since the experimental gas mixtures were delivered to the subject via oral-nasal masks, and the compression chamber was filled with air or low oxygen partial pressure, N_2-O_2 mixtures, a special procedure was utilized to insure that the experimental gas was in the spirometer as well as the divers' lungs. The two-inch rubber hose connected to the wedge bellows had a standard Collins 3-way T-respiratory valve connected to the mouthpiece end. A paper medicine cup with the bottom removed was used as a mouthpiece. The valve was closed, and the bellows were flushed from a high pressure line of the experimental gas mixture and exhausted to an overboard dump. The subject would hold his breath, remove the mask, place the mouthpiece valve in his mouth, hold his nose, open the valve,

perform the test, hold his breath, close the valve, and place the mask on his face. After this procedure, the spirometer was reflushed for a repetition or the next maneuver. When hydrogen-oxygen was used as the breathing medium, special precautions were taken to minimize contamination of the chamber with hydrogen.

Use of the Doppler Flowmeter

On-site doppler technique monitoring was provided during this program for the detection of circulating gas emboli in the blood vessels associated with decompression sickness. In addition to the opportunity to provide data correlating detection of Bubbles (and/or other artifacts) with this unit and observable or reported bends symptoms in the slowest or slower bodily tissues during the dive series, it was hoped that such detection would provide information which would aid in the evaluation of schedules previously untested which were intended to be modified as required to produce equivalent decompression stresses with N_2-O_2 and He-O_2 exposures, as compared with H_2-O_2 dives in the planned series.[2] In addition, on-site recordings of blood flow produced by an experimental precordial doppler ultrasonic bubble/blood flow detector were gathered for later spectrographic analysis and interpretation at NSMRL.

Tape recordings were made of selected samples of doppler signals produced during pre-dive, bottom, staged ascent, and post-dive conditions in the test series. Recorded signals monitored on site by Dr. Sergeant were later listened to and evaluated at NSMRL by LCDR Adams, Sergeant, Jensen, and Dr. Williamson. In conjunction with this auditory monitoring, samples were selected and submitted to spectrographic analysis in order to relate the acoustic character of doppler signals to clinical auditory interpretation of these signals and to document acoustic variations of doppler signals which are associated with the heart function. A manuscript proposed as an NSMRL report summarizes the results of this work (Adams et al., 1973).[45]

Speech Study Correlation with Mass Spectrometer

Breath-by-breath concentrations for six gases of an alveolar sample taken after selected speech test words have been given to Dr. Russel L. Sergeant so that he may calculate the density of the gas in the lungs and correlate this density with his work.

HYDROGEN-OXYGEN DIVES

Within two hours prior to the start of pressurization, a blood sample was taken from the diver. In addition, surface

speech recordings, pulmonary function measurements, performance measurements (short term memory, signal detection, mental arithmetic, and sentence comprehension), doppler flowmeter recordings, and pre-dive briefings were administered to the diver during this period.

Three minutes before the start of the dive, the subject would enter the air-filled chamber and commence breathing from a supply of 80%He-20%O_2 15-30 seconds prior to compression. The diver remained on this breathing mixture for one minute while the chamber was pressurized to 4 ATA with pure nitrogen. Upon reaching 4 ATA, the diver was switched to a mixture of 97%He-3%O_2, while the compression with nitrogen continued until a pressure of 7.06 ATA was achieved. Although the diver was switched to a 97% He-3% oxygen breathing mixture at approximately 4 ATA, about 15 seconds were required to purge the breathing line of the previously supplied mixture. In addition several respiratory cycles would be required to effect a gas exchange in the lungs which would approximate the breathing mixture supplies. During this time compression was continued from 4 to 7 ATA so that effectively the oxygen partial pressure would be expected to be maintained at normoxic to hyperoxic levels during the final minute of descent. Total descent time was 2-1/4 minutes $\pm$ 15 seconds. When the oxygen monitor indicated less than 4% O_2 in the chamber atmosphere, the diver was instructed to switch to the hydrogen-oxygen breathing system, and when the Douglas bag had filled to 50% of capacity, the dump system was activated.

During his exposure at 7.06 ATA, the previously described performance measurements, pulmonary function measurements and speech studies were performed. In addition, inspired and expired gas samples were continuously analyzed by the mass spectrometer via a nasal catheter, and the subject was required to complete a work load consisting of lifting and lowering a 40 pound weight 1 and 1/2 feet 420 times.

Five minutes prior to the initial reduction of pressure following the period of time spent at 7.06 ATA, the subjects were shifted to the main breathing system containing 97%He-3%O_2. During this time, the chamber was purged with pure nitrogen (to eliminate any hydrogen which might have been admitted to the chamber atmosphere), and finally, air was added to the chamber atmosphere to increase the oxygen level (now lowered as a result of the nitrogen purge) to a sufficient

value which would sustain life in the event that the chamber atmosphere had to be used as an emergency breathing mixture. One minute prior to leaving 7.06 ATA the subject was shifted to a mixture containing 80%He-20%O_2, which was used during the initial stages of decompression.

The subjects were decompressed in accordance with the schedule shown in Table 3. Except as indicated, the final 15 seconds of the decompression stop was used to bring the diver to the next decompression level. This schedule was used in connection with all 8 dives made with hydrogen-oxygen.

Following the completion of the dive, the subject remained in the immediate vicinity of the test chamber for a period of 6 hours, accompanied at all times by an attendant (who was a member of the test subject population), and thereafter was required to be within one hour's travel of the chamber area for a period of an additional 18 hours. During the first hour following the subject's arrival at surface pressure, pulmonary function measurements, speech recordings, and doppler flowmeter readings were made.

HELIUM-OXYGEN DIVES

The eight helium-oxygen dives involved the same procedure as those of the hydrogen-oxygen series except for the following deviations:

1. The exposure time utilized a breathing mixture of 97%He-3%O_2 in place of the hydrogen-oxygen mixture used in the previous series.

2. The chamber atmosphere consisted of air (instead of 97%N_2-3%O_2) at all times during this series.

3. The decompression schedules for helium utilized two tables (see Table 4), one table having the same total decompression time as hydrogen-oxygen (with a slightly different time-depth distribution in view of the differences with respect to solubility between the two gases) and a second decompression table with the total time reduced by 25 minutes as compared with the hydrogen-oxygen table.

4. Special precautions to insure safety of the chamber atmosphere for use with hydrogen-oxygen mixtures were omitted.

5. The 80%He-O_2 mixture was used for the entire period of descent from 0-200 FSW.

In the eight above-mentioned helium-oxygen dives, each subject was exposed to each of the two decompression tables shown in Table 4.

NITROGEN-OXYGEN DIVES

The eight nitrogen-oxygen dives involved the same procedures and personnel as in the helium-oxygen series with the following exceptions:

1. The entire exposure time at 200 FSW was planned for a breathing mixture of 97%N_2-3%O_2 with the exception of the last minute of bottom time, during which the diver was to breathe air.

2. Air was used during the descent from surface to 200 FSW.

3. No helium-oxygen or helium-nitrogen-oxygen mixtures were to be used during the period spent under pressure unless required for therapeutic purposes.

4. Decompression profiles were calculated for nitrogen-oxygen mixtures.

5. Planning and briefing of test chamber and test subjects on handling possible problems arising from narcosis and/or the "Chouteau" effect including the supply of hyperoxic $He-O_2$ mixtures as standby breathing mixtures.

Three decompression profiles were used in this series as shown in Table 5. Each of the four subjects made two nitrogen-oxygen exposures. Two of these subjects were decompressed each time in accordance with the second schedule. One test subject was decompressed once on Schedule #1 and once on Schedule #2. The remaining subject was decompressed once on Schedule #2 and once on Schedule #3.

RESULTS

The eight manned dives using a hydrogen-oxygen breathing mixture (as shown in Table 6) resulted in 50% incidence of bends. In each case decompression sickness symptoms occurred on surface, usually between 6 to 12 hours after leaving the chamber. In each case the pain was reported as occurring in one or both knees. In all cases the subjects were recompressed to 60 FSW and decompressed in accordance with U.S. Navy Treatment Tables.[46] Relief of pain occurred during recompression in all cases, and pain did not recur either during or following the treatment table used.

None of the four dives in which helium-oxygen Schedule #1 was used resulted in symptoms of decompression sickness; however, decompression sickness occurred following three out of the four dives (75% incidence) in which decompression Schedule #2 was utilized. In all cases the pain was reported to occur in one knee, and symptoms usually occurred within one or two hours after the subject reached surface pressure. The symptoms spontaneously regressed while at surface pressure, and none of the cases were treated by recompression therapy.

In the initial dive of the nitrogen-oxygen series in which decompression Schedule #1 was used, symptoms of decompression sickness occurred at the 40 FSW level in the left elbow of the subject. Complete remission of symptoms occurred during the period of residence at 40 FSW. The decompression schedule was followed to the surface (with the addition of 34 minutes at 5 FSW on oxygen), with symptoms recurring upon arrival at each new pressure level (including surface) and remitting during the period spent at each decompression level.

Decompression sickness occurred in three of the six cases (50% bends incidence) in which Schedule #2 was used. All were reported as knee pain occurring over one hour after the subject left the chamber. Of the three (3) cases of decompression sickness, one subject's symptoms were relieved once he was recompressed to 60 FSW on a modified Table 5, with the time spent at 60 FSW in accordance with treatment Table 5 and the time spent at 30 FSW in accordance with Table 6. The symptoms did not recur either during or following the prescribed treatment table.

This same subject (S.A.) was decompressed from his second nitrogen-oxygen dive in accordance with Schedule #3. Although the symptoms took longer to develop (over 6 hours), pain occurred in one knee and required recompression. The above-mentioned modified oxygen treatment table was again used with the same results.

The occurrence of decompression sickness by regimes given in Table 7 is restated in Table 8 in terms of incidence of decompression sickness by regimes.

Of the four subjects, two, P.G. and M.E., had an overall bends incidence of 66.66% and 50% respectively. One subject (S.A.) had symptoms of decompression sickness after every dive in the series except the one in which $He-O_2$ Schedule #1 was used. The remaining subject (P.M.) had no decompression sickness on any of the six dives in which he participated. The occurrence of decompression sickness according to the subject population is shown in Table 9, and the vital statistics of the subject population are shown in Table 10.

Other than the occurrence of decompression sickness symptoms, no unusual reactions (observable or subjective) were reported in connection with any of the helium-oxygen or hydrogen-oxygen dives. As might be expected, the subjects were observably narcotized, and the subjects reported that they were aware of this while breathing nitrogen-oxygen mixtures. In addition, two of the subjects (P.G. and M.E.) reported feeling nauseous and dizzy while breathing the nitrogen-oxygen mixture during their initial N_2-O_2 dive. In addition, one subject (M.E.) vomited during the exercise period on this occasion. Both subjects had eaten a heavy breakfast before entering the chamber as opposed to the two other subjects who had eaten nothing or had had a comparatively light breakfast on the same occasion.

In both cases of nausea, relief was obtained during the bottom period after the subjects were switched to the initial breathing mixture in the chamber (containing 10-15% oxygen in nitrogen), which was enriched with oxygen (to a maximum of 20%) during the remainder of their period of residence at that depth (7.06 ATA). Prior to the second nitrogen-oxygen exposure, the subjects previously afflicted were asked to eat a light breakfast prior to making the dive. On this occasion one subject (P.G.) reported only a comparatively mild sensation of nausea, and the other subject reported no symptoms.

With respect to the hydrogen-oxygen system and operation, no difficulties were encountered on H_2-O_2 dives. Prior to the start of the series all four test subjects had placed hydrogen-oxygen mixtures last in terms of their personal preference of the three breathing mixtures and placed helium-oxygen at first place on the list. After the completion of the series, three of the four divers indicated a preference for hydrogen-oxygen breathing mixtures over the other breathing

mixtures, with helium-oxygen taking second place. The remaining diver placed helium-oxygen first in terms of preference, while hydrogen-oxygen took second place.

PERFORMANCE MEASUREMENTS

Performances in the mental arithmetic tasks, short-term memory test, and signal detection task were impaired substantially at 200 FSW relative to those at control depth during the NITROX exposure, but not during the HYDROX or HELIOX exposures. There was no reliable change in performance of the sentence comprehension test under any circumstances from control levels.

Mental Arithmetic. The effects of test administration depth and inert gas respiratory medium upon mean error in addition-subtraction are shown in Figure 3. Analysis of variance (ANOVA) confirmed the implication of the figure that performance deviated from the control level only during exposure to NITROX at 200 FSW. Neither the simple effect of gas, nor that of depth were statistically significant; but the interaction between gas and depth was, $F(4,12) = 3.95$, $p \leq .05$. The major finding for the multiplication task, illustrated in Figure 4, is substantially the same. The major contribution to the highly significant interaction between gas and depth, $F = 20.64$, $p \leq .005$, is clearly the high error rate on NITROX at 200 FSW. The significant gas effect, $F(2,6) = 6.73$, $p \leq .05$ reflects the essentially artifactual depression of performance with NITROX by averaging over all depths, and the significant depth effect, $F(2.6) = 7.26$, $p \leq .025$ results from the general superiority of performance in the pre-dive test.

Short term memory. Error scores were obtained for each of the four tests within each dive. The mean error scores for all subjects combined are plotted in Figure 5. These curves indicate that little or no performance decrement occurred with either the HYDROX or HELIOX exposures, but a large decrement occurred during the NITROX dives.

The mean error scores for the two dives with the same gas mixture were calculated for each of the four tested depths for each subject. A three-way ANOVA on these means confirmed that there was:

(1) a significant gas effect, $F\ (2,6)=15,31, p < .005$
(2) a significant depth effect, $F\ (3,9)=9.31\ p < .005$
(3) a significant interaction between gas and depth, $F(6.18)= 3.48, p < .025$.

Newman-Keuls tests on the means shown in Figure revealed that the error score of the NITROX exposures at 200 FSW differed from all others at $p < .01$. No other differences among the means were significant.

Signal detection. The data for each S were subjected to signal detection analysis. Similar computations were made over all S's. The results indicated that Ss were rating their responses in a completely random manner. An additional analysis was therefore performed to obtain percent correct responses for each dive regardless of rating. The results of this analysis are summarized in Table 11. With the exception of a decrement in performance for NITROX at 200 FSW performance was similar under all conditions.

Sentence comprehension. Results were combined for the two sets of dives and data for each subject shown in Table 12. Averages over subjects are also shown. Both the number of sentences attempted and the percentage of these which are correct are shown.

BIO-CHEMICAL OBSERVATIONS

Decreases in whole blood clotting times were regularly observed during periods of exposure to the increased pressures of the simulated diving environments. While the phenomenon occurred during exposure to each of the gas mixtures, this development has not, to our knowledge, been previously reported. It may be an artifact induced by performance of the measurement under pressure, and therefore not be of in vivo significance.

A slight tendency toward increases in hemoglobin and hematocrit concentration--apparently resulting from hemoconcentration--was evident particularly after the hydrogen dive series. Hemoconcentration is a common by-product of hyperbaric exposures, and as with most of the bio-chemical and hematological data, does not necessarily indicate that aberrant physiological states were produced by the experimental procedures. Trends toward thrombocytopenia and hypofibrinogenemia followed the hydrogen dives. Because of the lack of sufficient data, evaluation of these responses can not be made for other diving experiments.

Complexities of the urine data will not allow satisfactory conclusions to be drawn until computerized statistical analysis are completed.

PULMONARY FUNCTION

Results of the control on air at the predive surface, at 200 FSW (on HYDROX, HELIOX, and NITROX), and at post-dive surface are given in absolute numbers and percentage of surface control (means of four) shown in table 13. All other depths and mixtures are reported as a mean of the individual percentage of surface control values, since there was a variable number of data points (from one to three). The control vital

capacities were 4.52, 4.41, 4.02, and 5.34 liters for the four men. It would be misleading to use a mean of all four for one condition and the mean of the first three for another condition, for example. This data is from four H_2-O_2, two He-O_2, and two N_2-O_2 dives. All divers had healthy lungs as judged by FVC, FEV_1/FVC, FEV_2/FVC, MEFR, and MVV values.

DOPPLER STUDIES

The two initial schedules in which the Doppler flowmeter was used resulted in "clean" dives, i.e., the absence of any symptoms of decompression sickness. The results of direct on-site monitoring, later monitoring of tape recordings, and spectrographic analysis indicated that no bubbles were detected with the experimental doppler unit over the precordial area of the diver's heart during any of the HYDROX, HELIOX, or NITROX dives studied.

MASS SPECTROMETER

There were no nitrogen "bursts or spikes" as previously observed by Schaefer and Dougherty (1974).[47] A more detailed analysis of the respiratory gas-monitoring data has not been accomplished yet, and further results cannot be presented until this is done.

DISCUSSION

PERFORMANCE MEASUREMENTS

Demonstration of performance decrements in the mental arithmetic and short term memory and signal detection tasks during exposure at 200 FSW to NITROX, but not to HYDROX or HELIOX, confirms expectations based on the diving literature, e.g. Bennett (1967),[9] and the general experience of the diving community. Failure to find such effects would have suggested that the dive profile was too innocuous to test the feasibility of a hydrogen based diving system. Conversely, appearance of performance decrements during either the HYDROX, or HELIOX, exposures would have implied that uncontrolled, or unrecognized, factors had rendered the findings invalid for assessment of hydrogen systems per se. Given the frankly experimental nature of the exposures and the anxiety in some quarters over use of hydrogen, disruption of performance by a generalized stress reaction was considered possible. Although bends incidence was relatively high in this study, there seems to be no direct relation to performance. First, performance decrements appeared reliably only with NITROX while bends struck following exposure to all three inert gases. Second, with one exception, bends symptoms were reported only subsequent to return to a 1 ATA air environment.

Mental arithmetic. Of the performance measures used in this study, the mental arithmetic tasks have the most substantial record for sensitivity to inert gas narcosis. Both forms showed man's capacities are impaired by a NITROX environment equivalent in nitrogen partial pressure to exposure to air at over 240 FSW. Neither test provided any evidence of deleterious effects of either the HYDROX, or HELIOX, environments employed.

Short Term memory. The short term memory test was highly sensitive to narcosis effects. Performance on the HYDROX and HELIOX mixtures were shown to be virtually indistinguishable with no significant decrement at 200 FSW as compared with pre-dive baseline measures. As expected, the NITROX mixture produced a highly significant performance decrement at depth due to narcosis.

An additional point of interest can be noted at the 10 FSW decompression stop of the dives. The elevated mean error score shown here was entirely due to one subject who experienced additional stresses on both of his NITROX exposures. On the first dive he experienced bends symptoms and on both occasions, severe gastric distress while at 200 FSW. These may well have caused his increased error scores during decompression. Although this elevated mean for all four subjects was not significantly different from any other mean (except the 200 FSW NITROX), it does provide further evidence of the short term memory test's sensitivity to stressful conditions.

Signal detection. Analysis of the data within the frame work of signal detection theory yielded results which did not differ from chance. Since the data was the same for both practice and dive sessions, these results must be attributable to factors other than the experimental conditions, i.e. subject and/or procedural variables in relation to the rating process. Considering the data in terms of percent correct responses, at 200 FSW performance fell off approximately 5% from pre-dive levels under NITROX (Figure 6). There were no other meaningful effects.

Sentence comprehension. As can be seen from Table 17, subjects 1 and 2 performed extremely well while subjects 3 and 4 were at chance (50%). That the task would be so difficult for any subject was not anticipated, and hence the results were not scored until near the end of the first cycle of dives. When it was clear that subjects 3 and 4 were doing so poorly, special instructions were sent to the dive supervisors to have them work with these two subjects so that they might improve their performance. This did not work. Subject 3 increased his percentage of correct answers from 51 to 52% in the second cycle while subject 4 went from 45% to 49%.

Why this task was so difficult for these subjects while it was so easy for the other two is a mystery, but this certainly suggests that the task may be somewhat limited in its usefulness.

The data for percentage of correct answers shows a slight effect for nitrogen narcosis, in that there is a small depression of performance at 200 FSW with NITROX but not anywhere else. This effect is not statistically reliable, and of course is gainsaid by the chance-level performance of two of the subjects. The number of items attempted did not vary systematically with any of the independent variables. Thus, the task was not very informative in this series of dives.

Pulmonary Function. A review of the data shows that all flow-related parameters (MVV, MEFR, and MIFR) increased at 200 FSW with H_2-O_2 as compared with surface air controls. There was some reduction with He-O_2 and considerable reduction with N_2-O_2 at 200 FSW. This result is of considerable importance in terms of respiratory limitations to work at depth.

The extent of this limitation varies according to density of breathing mediums, severity of work, lack of pathology in divers' lungs (pathology does occur sometimes), and to some extent, the investigator one is consulting.

The joint diving study at the University of Pennsylvania in 1971, reported by Lambertsen et al. (1972), showed that well-trained, above-average physical specimens can do useful work during acute exposures while at a simulated depth of 1200 FSW in a dry chamber breathing a neon-oxygen mixture equivalent in density to He-O_2 at 5,000 FSW.[18] Wright Peterson and Lambertsen (1972) had shown, when testing 19 gas mixtures with densities ranging from 0.4 to 25 grams/liter (equivalent to helium at sea level to helium at 4,983 FSW), that function at rest is not severely affected by the great density increase.[48] Respiratory limits to forced or exercising ventilation do appear, but use function persists even to the maximum density studies and can be predicted to persist to even much greater densities. However, Hyacinthe and Broussolle (1972) concluded that the limit of ventilatory capacity at work probably occurred at about 61 ATA of 2013 FSW of water.[49] The EDU-Taylor Study reported by Spaur (April-May, 1973) at 1600 FSW showed no problems at rest, but some dyspnea during mild to moderate exertion in the wet pot using a modified MK10 MOD 4, closed-circuit, mixed-gas, underwater breathing apparatus.[21] The apparent increase in FVC during H_2-O_2 and He-O_2 dives at 200 feet compared to air at the surface is difficult to explain. There is always the possibility of experimental error or a chance happening especially with limited data. A training effect is also a possibility, but this would not

explain the data later decrease in values to nearer control. The subjects were trained on days prior to the dive and my experience has shown little training effect on FVC in a healthy, motivated subject who is instructed and coaxed properly. There is also the possibility of an autonomic nervous system effect. Another possible explanation is the circadian cycle effect.[50] Some of the control data was obtained on days prior to the dive; it was always performed on the morning of the dive at 8-10 A.M., usually a couple of hours prior to compression. The post dive recovery data was done about 12 hours later at 9-10 P.M. usually.

Mechanical respirators add a load not encountered in some experimental studies in dry chambers with pulmonary testing equipment. In any case, one must conclude that ultimately there is a respiratory limit at some depth and some degree of work load. For a given depth, a greater ventilation is possible with a less dense gas during extreme exertion and/or emergency situations. Therefore, hydrogen-oxygen has some significant advantages from a pulmonary point of view.

DOPPLER AND MASS SPECTROMETER DATA

Relative total body gas exchange ratios for the inert gases studied require a more detailed analysis which has yet to be accomplished of the gas monitoring data. However, no nitrogen "bursts or spikes," as previously observed by Schaefer and Dougherty (1973),[47] were observed during the dives in this program. Similarly, no "bubbles" were heard on the doppler ultrasonic system. In the case of the doppler system, it must be noted that in all but one instance, clinical symptoms did not arise for several hours after doppler measurements were normally scheduled, and by the time the doppler unit was rushed to the subject who "bent," all clinical symptoms of decompression sickness had disappeared. The subjects were periodically monitored, however, for one hour or more following the final decompression stage to sea-level. If, as Nims (1951)[51] suggests, bubble growth occurs for some time before clinical symptoms appear, some indication might have been expected during this period of bubble growth. Optimum conditions for bubble formation occurred upon the arrival of the subject at a new pressure level during stage decompression procedures, since at this time the greatest inert gas volume is present in the tissues. During the subsequent stay at a given pressure level, the inert gas is eliminated by the body, with corresponding decreases in the supersaturation ratio in a given tissue site of any compartment (in which the inert gas partial pressure is initially in excess of the partial pressure in the inspired breathing medium), thereby reducing the conditions favoring bubble formation.

Following the formation of a bubble within a given tissue compartment, growth should occur until maximum bubble pressure

or clinical symptoms occur and are treated by recompression. This presupposed existence of sub-clinical or "silent bubbles" as strongly indicated by evidence summarized by Behnke (1969).[52] If we accept the existence of sub-clinical bubble formation during the initial hour of the post-dive period, it can be argued that bubble size during this period was too small to be detected. This argument, however, fails to explain the inability to detect bubbles in the one subject in which symptoms occurred under pressure and recurred after arrival at subsequent decompression stops.

The failure to detect bubble formation in the latter case, and probably in the former cases as well, may be related to the inherent limitation in such detection by the nature of the device itself and by the difficulties posed by the probable sites of bubble formation within the body. The doppler system is designed to detect moving bubbles in the bloodstream within the specific area dictated by the placement of the probe (in this case the precordial area). The ability of this system to function in such a manner as to indicate the presence of bubbles prior to or in connection with symptoms of decompression sickness is predicated upon the assumption that such bubble formation will be intravascular.

Measurements of nitrogen washout time of the blood made by Ferris et al. (1951) indicate the time constant of blood to be about 5 to 10 minutes for most conditions.[53] Such a tissue would be totally saturated with inert gas long before the completion of the 120 minute bottom time required in the pressure profiles used in this experimental series. Further, much slower tissue compartments would be so high at the end of this bottom period that they would control or limit the initial ascent to the first stages of decompression. Since the safe supersaturation ratio or M-value that could be tolerated by slower compartments is much lower than the permissible ratio's or M-values which could be tolerated by the faster tissue compartments, such compartments do not attain values appreciably near previously demonstrated safe limits, and hence would not be expected to be the sites of bubble formation.

When decompression sickness results in tissue half-time compartments other than the fastest or faster compartments, consideration must be given to the possibility that such bubble formation may be extravascular. Over 50 years ago, Haldane (1922) and others considered the possibility of extravascular bubble formation being responsible for some types of decompression sickness.[54] The probability for extravascular bubble formation in the slowest bodily tissues would appear to be very high in profiles in which the slowest tissue compartments controlled or limited decompression, as was the case in the final stages of the decompression schedules used in these tests.

Pain in one or both knees is the characteristic symptom reported from such exposures in which violation of safe M-value or supersaturation limits occurs. The extremely long half-time associated in the slowest compartment, and hence the knee joints, is comprehensible only in relation to the highly avascular tissue (existing at these anatomical sites) which would be logical focal points for bubble formation. One would expect, therefore, that any injury and/or surgical intervention in this area which would be expected to alter and reduce the perfusion in said area would increase individual susceptibility to decompression sickness in profiles involving the slowest tissue compartments. Accordingly, in the present series and in one experimental series involving decompression following total saturation exposures with nitrogen-oxygen mixtures for PROJECT TEKTITE I (Edel, 1971)[55] the most susceptible subjects were the individuals who had histories of severe leg injuries.

Such extravascular bubble formation offers a possible explanation for lack of detection of bubble formation with the doppler flowmeter. Such bubbles would neither be in motion nor in the bloodstream, the two conditions required for doppler detection.

If extravascular bubbles exist, the probability of their occurrence would generally increase with increases in tissue-half-times and, therefore, the probability of detection by means of a doppler system would decrease accordingly. While the evidence is far from conclusive, the inability of doppler monitoring to correlate with bends symptoms resulting in this dive series suggests that particular attention should be directed towards utilization of the doppler flowmeter in future experiments involving the slower and slowest tissue compartments. Particular attention should be made in such tests that the faster compartment safe limits are not violated in the early stages of decompression, since this could produce erroneous results in data subsequently correlated with slower compartment half-times.

INITIAL DIVES WITH DOPPLER FLOWMETER

The two schedules initially used in this series with the doppler flowmeter had been extensively tested prior to the start of this program. In the case of the repetitive air schedule (See Figure 1) only one case of decompression sickness had been observed in over 50 tests of this profile. The direct ascent to the surface following the second two-hour exposure at 47 FSW resulted in high, but acceptably safe, tissue tensions in the slower, although not the slowest, bodily tissues.

In contrast, the multiple inert dive to 250 FSW (See Figure 2) involved the fastest and faster bodily tissues during decompression to the surface. This dive had also been extensively tested and has not, to date, resulted in a single case of decompression sickness.

Since the use of the doppler flowmeter in one of each of these dive profiles did not result in symptoms of decompression sickness, it was assumed that no experimental safety problem was associated with this unit for the purposes of this project. Accordingly, it was used to monitor all subsequent dives in this series. Although only two tests were involved, there was no suggestion that the sonic energy of the doppler flowmeter produced any intravascular bubbles, or bubble enhancement via cavitation, which would in effect alter a subject's response to decompression sickness.

Subjects relative susceptability to Decompression Sickness

In contrast to the subjects troubled by symptoms of decompression sickness, subject (P.M.) was highly resistant, remaining symptom-free in all of the six dives in which he participated. The remaining subjects represented the midpoint between these extremes, accounting for slightly less than 60 percent of the incidence of bends and requiring one treatment table each.

If the subjects (S.A.) and (P.M.) had been eliminated from the program, along with the questionable profile of nitrogen-oxygen Schedule #1, the results would have been essentially unchanged. The remaining subjects would have still accounted for approximately a 50% bends incidence with each gas mixture and, therefore, for a total bends incidence of 50% for all breathing mixtures.

NITROGEN-OXYGEN DECOMPRESSION SCHEDULES

The reaction of two of the subjects (severe nausea and vomiting in one case) while breathing nitrogen-oxygen at 7.06 ATA was so severe as to require an elimination of portions of the assigned work loads and testing programs. In the initial experiment both subjects had eaten a hearty breakfast prior to the start of the experiment. When the experiment was repeated with these subjects on the second occasion in which no breakfast was consumed prior to the dive, the symptoms were greatly diminished in one subject and barely noticeable in the second (who had vomited on the previous occasion). In all cases relief was obtained by breathing the chamber atmosphere, which was identical to the breathing mixture except for increased oxygen partial paressure. No problems of this nature were experienced by any of the subjects during exposures with helium-oxygen or hydrogen-oxygen in which the oxygen percentage in the breathing mixture was the same (3%) as in the nitrogen-oxygen breathing mixtures. Hence, the reaction was due solely to the nitrogen-oxygen breathing mixtures.

That nitrogen in itself could be the cause of this phenomenon would appear to be extremely doubtful in view of many exposures made to depths of 250 FSW or greater with air breathing mixtures in which the nitrogen partial pressure was equal to or exceeded the N_2 partial pressure in the subject's breathing

mixture during these tests (226 FSWA equivalent to an air mixture at a depth of 250 FSW).

It would appear that the only unusual feature in this case is the P O_2 level, which was much lower than that normally used with nitrogen at this depth. In exposing goats to normoxic helium mixtures at depths of between 1280 and 1820 FSW, Chouteau et al. (1967)[22,23] observed intermittent paresis of the hind limbs developed at pressures in excess of 1600 FSW, which was reversible upon an increase of the oxygen partial pressure in the breathing mixture. In an effort to correlate this effect with gas density, which also was reversible after elevating the P O_2 in the mixtures, Chouteau observed similar effects with normoxic nitrogen mixtures at a depth of 320 FSW. The investigators postulated possible disturbances of the alveolar-capillary exchange, a decrease of pulmonary diffusion of oxygen and/or an alveolar-capillary block altering the ventilation perfusion ratio. In addition, Lanphier suggested the possibility of oxygen-diffusion deadspace as a possible cause.[56]

In this experiment, we have similar circumstances involving a normoxic mixture coupled with high gas density, while the breathing resistance was increased by the use of the oral nasal mask. The effects were found to be reversible by an elevation of P O_2 in the inspired breathing mixture. In addition, the effect was observed to be more severe when the subjects had eaten heavily (increasing substantially the metabolic oxygen requirements of the subjects) as compared with fasting just prior to the experiment. This finding might suggest hypoxia as a possible cause of the symptoms occurring during this exposure.

The decompression sickness resulting from the initial dive in this series (See Figure 7) using Schedule #1 has no direct bearing upon the subsequent analyses of relative inert gas transport mechanisms, since the latter are concerned with an evaluation with respect to the slowest bodily tissues. The initial symptoms, in this case, were reported under pressure, 40 FSW, suggesting precipitation of the condition at an even greater level. Further, the reported location of symptoms (elbow) is not associated with symptomatic response from decompression sickness in which the slowest tissues are affected. The location, character, and response of these symptoms (particularly the remission of symptoms during the time spent at each pressure level) were most suggestive of bubble formation affecting the faster bodily tissues. Accordingly, this schedule was recalculated to include more additional time at the deeper stops to reduce the supersaturation ratios of the faster tissues; additional time at the shallower levels was required to compensate for the additional gas uptake in the slower bodily tissues caused by the increased exposure to positive N_2 gradients in the slower compartments. The absence of any symptoms involving the faster tissues in the remainder of the nitrogen-oxygen exposures was evidence that the schedule accomplished the required adjustments.

The symptoms in the remainder of the dives were exclusively reported as knee pain, occurring one or more hours after reaching surface. This is characteristic of decompression profiles in which bubble formation in the slowest tissues has occurred. Clearly, this schedule is a borderline table producing bends in roughly half of the subject population involved in the 7 hour and 52 minute ascent to surface.

The calculations which computed this schedule utilized the traditional Haldane compartments (with the addition of slower tissue half-times) together with M-values similar to Workman's (1965) [57] and the classical uptake and elimination equation $P_t = P_0 + ((Pa-P_0)\ (1-e^{-kt}))$, of which the components may be defined as follows:

P_t: The final nitrogen partial pressure in feet sea water absolute (FSWA) in the tissues after an exposure to P_a for t minutes.

P_0: The original tissue partial pressure of nitrogen in FSWA before the exposure.

P_a: Partial pressure in FSWA in the breathing medium.

e: Base of natural logarithms.

t: Exposure time in minutes.

k: $\frac{0.693}{t\ 1/2}$ (tissue time constant)

0.693: Logarithm to the base e of 2.

Calculations assumed nitrogen to be the only gas to be considered, with oxygen contributing no part of the gas volume in any compartment nor having any effect upon bubble formation. The same assumption was carried out in the calculations of dives using other inerts in this series. Since, as can be seen from Tables 3, 4, and 5, the same oxygen percentages were used at the same depths, in all dives in this series, any contributing effect resulting from oxygen would cancel out between dives with the varying breathing mixtures.

Whenever pure oxygen was used during decompression, it was considered to be 80% effective. Hence P_0 during oxygen breathing was calculated as if the inert percentage had been 20%.

With the aim of isolating the final stage of decompression to the surface as the level in which bubble formation was precipitated, the tables were constructed to overcompensate for the decompression obligation preceding the reduction of depth at the shallower levels (not including the final decompression stage) to prevent the possibility of bubble

formation at depth. This was done in all cases so that decompression sickness symptoms resulting from a single pressure reduction stage could be evaluated as common to all cases of dives performed in connection with this series.

Since the experience of Projects TEKTITE I and TEKTITE II had indicated that half-times in the order of 500 minutes had to be considered in calculating decompression tables from a state of total saturation with nitrogen in the bodily tissues, a time constant of 480 minutes was included.[58,59] In addition, some experiences (involving minor symptoms not requiring recompression) suggested that perhaps longer tissue-half times should be taken into account, and, accordingly, a hypothetical nitrogen half-time compartment of 720 minutes was added to the list. In order to represent faster tissues that could be involved in producing decompression sickness upon surfacing, 300 and 360 minute tissues were also added.

Using these values, the calculations indicated the following tissue tensions upon arrival at surface pressure following the nitrogen-oxygen decompression Schedule #2.

Table 14

Compartment half-times	300	360	480	720
Surfacing tissue tensions (FSWA)	46	46.8	46.5	43.6

From these figures it would appear that the 360 and 480 minute tissues were the compartments involved in the decompression sickness symptoms experienced by the test subjects. Whether or not a tissue slower than 480 minutes exists could not naturally be determined on the basis of this table, but this compartment was retained for subsequent evaluation in the schedules involving helium-oxygen and hydrogen-oxygen breathing mixtures, since in those cases the nitrogen tissue tensions could be added to the slowest tissues' helim and/or hydrogen fractions to conceivably produce a violation or limiting inert partial pressure in such a hypothetical tissue.

That nitrogen tissue tensions of less than 47 FSWA may still be unsafe upon a reduction to surface pressure may initially seem surprising. However, the experiences of TEKTITE I and II would seem to indicate either that extremely long, i.e., in excess of 500 minutes, half-saturation times were effecting the decompression requirements following dives in which the slowest bodily tissues were totally saturated with nitrogen, or, that much lower tissue tensions than had hitherto been anticipated could produce decompression sickness in the slowest tissue half-time compartments, or that the problems in computing such tables for the projects could have been some combination of the above factors.

Based upon these experiments it would appear that even tissue tensions of 47 FSWA are unsafe upon arrival at surface pressure and that a value of 46 FSWA or less must be achieved prior to any such pressure reduction.

The schedule used in the final dive in this series was identical to Schedule #2 except that it included an additional 20 minutes on oxygen at the 10 FSW level. This schedule was used to control the decompression in the second dive of subject (S.A.) who was at that time suspected of being the most susceptible member of the subject population to decompression sickness. Any change in the subject's response to this increased time was not discernible as compared with the previous schedule. In this case the nitrogen tissue compartment values upon surface were reduced to the following partial pressures:

Table 15

Compartment half-time	300	360	480	720
Surfacing tissue tensions (FSWA)	44.3	45.4	45.4	43

Obviously in this case, M-values less than 46 FSWA were still productive of decompression sickness symptoms, and surfacing tissue tensions would have to be reduced to values of 45 FSWA or less in computing nitrogen-oxygen decompression schedules for this individual.

HELIUM-OXYGEN DECOMPRESSION SCHEDULES

The helium-oxygen decompression calculations were carried out, for the purposes of analysis, on the same basis as the nitrogen-oxygen decompression calculations--with one exception. Obviously the same compartment half-time values cannot be used for helium and nitrogen because of the differences in uptake and elimination between these gases. If values of 500 minutes were assumed for helium-oxygen in the slowest bodily tissue, decompression from a state of total saturation would be impossible within the times accomplished for projects Sea Lab I and II. Such schedules were satisfactorily achieved using a slowest compartment half-time of 240 minutes, and such a value was accordingly used in helium half-time calculations for the purposes of analysis. While it seemed that slowest tissue half-times were non-existent for helium, inclusion of faster half-times values was required. It seemed reasonable to choose a half-time value of 180 (used by Buhmann in 1969).[60] In addition, the ratio of the partition coefficients of N_2/He (See Table 16) would suggest a value of about 160 minutes, assuming a slowest nitrogen half-time constant of 480-500 minutes. Since this value is uncomfortably close to the previously selected value of 180 minutes, a third value of 150 minutes was chosen.

Since the operative tissue tension value in producing decompression sickness must be some combination of the individual inert fractions (in this case $P_{He} + P_{N_2}$), it was necessary to identify compartments with respect to the corresponding helium half-times for the previously chosen nitrogen half-times. However, as previously explained, precautions were taken to eliminate bubble formation from all but the final ascent to surface. For the purposes of analysis, the helium values were left "floating" (not identified by compartments), to be combined in all possible combinations with nitrogen half-times at the end of the decompression calculations. As might be expected, the nitrogen component in the slowest compartments was considerable because of the periods of time spent at depth breathing nitrogen-oxygen mixtures during decompression from the helium-oxygen dives. In these dives, as in the previous series, the symptoms can be recognized as resulting from inadequate decompression in the slowest bodily tissue. With the use of helium-oxygen, Schedules I and II provide a comparison of relatively safe schedules; in Schedule I no decompression sickness resulted in any of the four dives made, and in Schedule II, a borderline schedule, three out of four dives resulted in decompression sickness (see figure 8). In the case of Schedule II, the symptoms result from inadequate decompression with respect to the slowest tissue half-time compartment.

With respect to the surface nitrogen tissue tensions in the previously selected compartments, the values were as follows:

TABLE 17

Compartment half-time	300	360	480	720
Surfacing P_{N_2} (FSWA) Sched. #1	20.1	22.5	22.9	22.8
Surfacing P_{N_2} (FSWA) Sched. #2	21.3	21.8	23.4	23.1

With respect to the helium half-time constants chosen the values were as follows:

TABLE 18

Compartment half-time	150	180	240
P_{H_e} surfacing values: Sched.#1	16.6	20.3	24.7
P_{H_e} surfacing values: Sched.#2	18.7	23.4	23.1

To examine all the possibilities for the purposes of elimination, we can combine each one of the hypothetical helium half-times

with each of the nitrogen half-times to produce the table shown in Table 19.

Prior to the next stage of calculations involving hydrogen--an attempt to apply hypothetical half-time values for H_2 (in which case, unlike the previous cases, we have no guidance from past experience to aid with the selection of half-time values)--some elimination of possible combinations must be made. Duffner and Snider (1958) demonstrated that safe helium surfacing tissue tensions were much higher than those for nitrogen.[61] We have already established from the previous experiment that a surfacing value of 46.8 FSWA is borderline (producing decompression sickness approximately 50% of the time) in cases when nitrogen-oxygen breathing mixtures are used. But referring to Duffner and Snider (1958),[61] we can see that the surfacing values must be higher with helium-oxygen breathing mixtures, and hence we can rule out any combination with a value of 46.8 FSWA or less in Schedule #2. This leaves us with the following possible combinations:

TABLE 20

COMPARTMENT #	A	B	C	D
N_2 1/2T Values	300	360	480	720
He 1/2T Values	240	240	240	240
P N_2 + He Sched. II	47.9	48.4	50.0	49.7

However, we can also rule out compartments A and B, since it is well established from the TEKTITE experiment that the slowest half-saturation time tissue with nitrogen must be at least approximately 500 minutes. This leaves us with two possible alternatives--the first, a nitrogen half-time of 480 minutes and a helium half-time of 240 minutes, and the second, a nitrogen half-time of 720 minutes and a helium half-time of 240 minutes. In any case, it would appear that the helium half-time in the compartment responsible for the symptomatic response of the subjects in the experiments previously mentioned must be approximately 240 minutes. Therefore we can reduce our previous number of choices to two alternatives, which permits us to examine hypothetical hydrogen half-times (based upon the results of the experiments in this program) in terms of these alternatives.

HYDROGEN-OXYGEN DECOMPRESSION SCHEDULES

Only one table (see fig. 9) was used in the hydrogen-oxygen dives, and all subjects decompressed in accordance with this schedule twice during this portion of the experimental series.

One subject (S.A.) reported symptoms of decompression sickness on each occasion, while subject (P.M.) had no symptoms following each of his dives. Each of the remaining two subjects made one dive which resulted in no symptoms and one dive which resulted in symptoms of decompression sickness. In all cases the symptoms were typical of inadequate decompression with respect to the slower (or slowest) bodily tissue compartments, and recompression therapy (U.S.N. Table 5) was given in each case in which symptoms occurred.

The surfacing values of the slowest tissue compartments with nitrogen are as follows:

TABLE 21

Nitrogen compartment half-time	300	360	480	720
Nitrogen tissue tensions (FSWA)	22.7	23.1	23.5	24.2

These values for helium are as follows:

TABLE 22

Helium compartment half-times	150	180	240
Helium tissue tensions (FSWA)	6	6.9	8.1

Adding the last compartment value for helium to the last two compartment values for nitrogen, we obtained P N_2 + He tissue tensions of 31.6 and 32.3 FSWA. Clearly, any compartments other than the slowest have lower tissue tensions, regardless of how we attempt to combine the tissue half-times for the two inerts. Hypothetical hydrogen half-times can then be drawn up and added to the sums (P N_2 + He of the slowest compartment for comparison. Unlike helium and nitrogen, there are no previously established surfacing values for hydrogen, and hence there are no standards for guidance in the proper selection of one or more possibilities from a spectrum of possible hydrogen limiting half-times. However, we can hopefully assume that hydrogen will be subject to the same patterns with respect to half-times and safe supersaturation limits which have been observed and corroborated by a large amount of data with regard to the previous mentioned gases.

If we compare the various tissue half-time compartments and their maximum permissible M-values as reported by Workman (1965)[57] we have the following table:

TABLE 23

Compartment 1/2T	5	10	20	40	80	120	160	200	240
M-value (N_2) (FSWA)	104	88	72	56	54	52	51	51	50
M-value (He) (FSWA)	86	74	66	60	56	54	54	53	53

It is important to note that when there is a measurable difference (one FSWA or greater) in the helium and nitrogen compartments, the permissible M-value decreases as the half-time increases in both cases. Although this progression holds true within the individual compartments for a given gas, the relationship, according to this table, would not appear to hold true with respect to one-half time per se in the two cases cited. However, experience has shown that a surfacing value of 53 FSW is indeed too high, and, as shown in the present series, a maximum value of 50 FSW appears to be borderline. In addition, in experiments by Edel, Honaker, Carroll, and Beckman (1969), subjects breathing air were exposed for 24 hours to pressures of 33 and 30 FWS and then proceeded by direct ascents to surface pressure during which the decompression was a function of the 240 minutes half-time compartment with nitrogen. The equivalent limiting value of nitrogen was also found to be about 50 FSW.[62] In the experiments in this series, we have seen that a much higher value, two to three times longer than helium half-times in the same compartment, for helium (with an assumed maximum half-time of 240 minutes) can be tolerated than for nitrogen (with a slowest tissue half-time). There is therefore evidence that the relationship (even when considered between these two gases) between permissible supersaturation (or M-values) may be much closer than is indicated by the above table.

If, then, the half-saturation time of the slowest tissue with hydrogen should be longer than that for nitrogen, we should expect a lower M-value than 46.8 FSWA. If the slowest half-time tissue with hydrogen should be shorter than that for helium (as a diffusion model would suggest) we should expect a higher M-value than 50 FSWA. Should the slowest tissue with hydrogen have a half-time between the nitrogen and helium slowest tissue half-times, (as a perfusion model would suggest), we should expect to find some corresponding M-value between 46.8 and 50 FSWA. The M-value for this tissue will, of course, be the sum of the individual components for helium, nitrogen and hydrogen. The values for nitrogen and helium in the two hypothetical slowest tissue compartment models have been calculated, and hydrogen fractions can be calculated from a spectrum of possible values to obtain total surfacing tissue tensions (P N_2 + H_2 + He) for evaluation.

In a diffusion-limited system, the slowest half-time tissue with a given gas would be indicated by the square root of the molecular weight. From the values shown in Table 16, we can see that nitrogen should have the slowest half-time tissue value of any of the gases listed. Hydrogen should have the fastest half-time value for the slowest tissue, and helium should lie in between the two. If helium is taken as a "standard" the value for the slowest tissue with hydrogen should be (from Table 24) 2.0/1.42, or 1.41, times faster than helium. Taking the helium time constant of 240 minutes and dividing it by this ratio gives a half-saturation time for hydrogen of approximately 170 minutes.

If a perfusion-limiting model is assumed, we can see from Table 24 that the slowest tissue half-time with hydrogen should be 1.8 times the value chosen for helium. With a helium half-time of 240 minutes this would give a value of 432 minutes for hydrogen. If some combination of perfusion and diffusion determines the slowest tissue half-time, the value should be between these two extremes. Should, for example, both factors have equal weight, the value would be 300 minutes for hydrogen, using the helium value as a standard.

Time constants of 170, 180, 200, 240, 300, 360, 430, and (as a comparison with the nitrogen time constant) 480 were chosen for calculation to determine the final M-value on surfacing from the dives in the hydrogen series in this program. Calculating the hydrogen schedule used in this series with the above time constants produced the M-values shown in Table 25.

TABLE 24

H_2 1/2T	170	180	200	240	300	360	430	480
P H_2 (FSWA)	11.8	12.6	13.9	15.7	17.0	17.6	17.4	17.0

Since the slowest tissue half-time with nitrogen and helium (from Tables 21 and 22) produced the highest surfacing values on this dive, (unless one assumes the slowest tissue with hydrogen to have a half-time of 480 minutes or longer), it is apparent from Table 25 that the slowest tissue with hydrogen is also producing the highest value, since whichever value is chosen (with the exception of the 480 minute half-time), all faster tissue M-values will be lower.

If we add these values to the compartment with a helium half-time of 240 minutes and a nitrogen half-time of 480 minutes (with a tissue tension P N_2 + He = 23.5 + 8.1 = 31.6) we obtain the following results:

TABLE 25

H_2 1/2T	170	180	200	240	300	360	430	480
P N_2+He+H_2 (FSWA)	43.4	44.2	45.5	47.3	48.6	49.2	49	48.6

If these tissues are added to a compartment with a helium half-time of 240 minutes and a nitrogen half-time of 720 minutes (with a tissue tension of PN_2+He = 24.2+8.1 = 32.3), we obtain the following values:

TABLE 26

H_2 1/2T	170	180	200	240	300	360	430	480
P N_2+He+H_2 (FSWA)	44.1	44.9	46.2	48	49.3	49.9	49.7	49.3

Assuming that a half-time with hydrogen which is equal to or faster than that for helium in the slowest bodily tissues would have a surfacing M-value of 50 FSW (or greater) eliminates the first 4 values in the above tables. At the same time, the M-values for the last two half-time values would appear to be obviously too high for such slow tissue half-times, as would the value for a 360 minute half-time hydrogen tissue in table 26. Even the lower value (in Table 26) would seem uncomfortably high (although perhaps not impossible) for a 360 minute half-time tissue, and 300 minutes (or some intermediate value between the two) would seem to be the most probable choice.

From the above data, it would appear that a model based upon a pure diffusion limited system would fail to explain such a tissue half-time (or range of possible tissue half-times) in the slowest compartment with hydrogen. The analysis would tend to indicate that either a perfusion-limited system or some combination of perfusion and diffusion governs gas transport in the slowest bodily tissues.

H_2-O_2 GAS HANDLING SYSTEM PERFORMANCE

Operational problems related to the use of hydrogen-oxygen mixtures in this experimental series were notable only by their absence, and the greatest difficulties resulted from diver-to-surface communication. In both the hydrogen-oxygen and helium-oxygen experiments, communication was possible but difficult without the use of any "unscrambling" device. However,

increased communication difficulties must be anticipated for depths much in excess of that used in this series and would require some form of an unscrambler to maintain adequate communication between the subjects and surface control.

CONCLUSIONS

1. The data gathered from this project can be utilized as a basis for further experiments with increased depths and/or exposure times.

2. Further experiments are required to examine the reaction of the human organism to hydrogen-oxygen at depths at which HPNS symptoms can be detected with helium-oxygen mixtures in order to further assess the maximum potential operational depth for these mixtures.

3. The slowest bodily tissue with hydrogen appears to have a half-saturation time of approximately 300 minutes.

4. The results of the experiment cannot be explained on the basis of a pure diffusion limited system for gas transport.

5. The apparent half-saturation time value with hydrogen in the slowest tissue suggests a perfusion or perfusion-diffusion gas transport mechanism.

6. Ventilatory ability with hydrogen at 200 feet of sea water equivalent is improved about 32% compared with helium and 152% when compared with nitrogen.

7. Communication difficulties with hydrogen appear to be approximately the same as for helium when the oxygen percentage is the same in both mixtures.

8. In calculating nitrogen-oxygen saturation tables, surfacing values of 46 FSW or less are required for asymptomatic return to sea level.

9. Surfacing values of less than 50 FSW are required for asymptomatic return to sea level pressures following helium-oxygen saturation dives.

10. There is a possibility that hypoxia may be encountered in human exposures with normoxic nitrogen mixtures at depths of 200 FSW or greater.

11. There are no apparent medical contra-indications to the use of hydrogen-oxygen breathing mixtures within the limits of this experimental series.

12. Because of what appears to be more rapid uptake and elimination times for helium as compared with hydrogen, great care must be exercised when attempting to switch from hydrogen to helium in order to prevent bubble formation which would result from a rapid intake of helium as well as the comparatively lower elimination of hydrogen in the tissues, a development which could lead to dangerously high M-values for P_{H_2}+He under certain conditions.

13. There are no noticeable changes in performance with hydrogen-oxygen as compared to helium-oxygen breathing mixtures, although nitrogen-oxygen mixtures produce an obvious decrement in performance when compared with either of these gas mixtures of 7.06 ATA.

14. No problems with respect to induced bubble formation or enhancement could be ascribed to the doppler flowmeter used in this experimental series.

15. The doppler flowmeter failed to detect any bubble formation in the bloodstream on occasions in which subjective symptoms of decompression sickness were reported.

16. Lack of correlation between detection of bubbles in the bloodstream and reported decompression sickness symptoms suggests the possibility of extravascular bubble formation in the slowest tissues as the cause for bends incidence in this experimental series.

SUMMARY

Since the world's supply of helium is diminishing, it is important to evaluate possible substitutes for helium in breathing mixtures for use in future deep diving operations. On the basis of its physical constants, hydrogen would seem to be the most promising replacement for helium as an oxygen dilutant for human exposures to very high pressures.

The experimental program involved four volunteer diver-subjects, each of whom was exposed on two separate occasions to 7.06 ATA for a period of 113 minutes whild breathing a mixture of 97%H_2-3%O_2. This experiment was repeated using 97%He-3%O_2 for a total number of 24 dives in which each subject was exposed to each breathing mixture twice during the program. During the exposures a work load was performed by the subjects and measurements were made. In addition, blood and urine samples were collected, a mass spectrograph analysis was made of the divers' inspired and expired breath, speech studies were conducted, pulmonary function measurements were made, and a doppler flowmeter was used to monitor the presence of bubble formation in the divers' blood stream during decompression.

Decompression profiles were adjusted during experimentation to produce approximately equal bends incidences for dives made on all gas mixtures. Subsequent analysis of dive profiles indicates the half-time for the slowest compartment with hydrogen to be slower than that for the same compartment with helium and faster than that for the same compartment with nitrogen. A tentative value of approximately 300 minutes is indicated for the slowest tissue half-time with hydrogen. This result would indicate that inert gas transport within the human body is not diffusion-limited and may be either perfusion-limited or affected by a combination of diffusion and perfusion.

Subjects whose dives resulted in decompression sickness were treated in accordance with U.S.N. Treatment Table 5 with complete success in all cases.

With the exception of decompression requirements (suggesting the necessity for a slightly longer decompression following hydrogen dives), all data gathered which has been analyzed indicates hydrogen to be equal or superior to helium for operations at the levels tested. The pulmonary function measurements in particular suggested benefits in the following:

(a) Deeper diving ability for a given work load

(b) Increased work performance at a given depth in comparison with helium.

Extrapolations to greater pressures are not possible with a high degree of confidence due to insufficient data pertaining to possible effects on the central nervous system with hydrogen under extreme pressures; however, the favorable outcome of experiments performed to date would indicate the desirability of further experimentation at higher pressures.

It is interesting to note that the doppler flowmeter failed to detect intravascular bubbles in any of the dive profiles used, including one dive in which the symptoms occurred under pressure. One possible explanation which would cover all dives made in this series is that symptoms were due to extravascular bubble development which would be indetectable to monitoring devices based upon the principal of the doppler flowmeter.

No difficulties were encountered in operational use of hydrogen-oxygen in experiments performed in the dry chamber. Since in open water the need to provide a safe atmospheric blanket within the chamber which would be non-flammable and non-explosive in contact with the breathing mixture and/or some form of overboard dump system would be eliminated, procedural problems would be vastly reduced.

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TABLE 1

MULTIPLE INERT TEST TABLE

DEPTH (FSW)	TIME (MIN)	BREATHING MIXTURE
0-150	1.5	AIR
150-250	1	50%He-50% AIR
250	5	"
250-190	1	"
190-70	2	AIR
70	1	"
60	1	"
50	2	OXYGEN
40	2	"
30	2	"
20	3.5	"
20-0	1	"

TABLE 2

Examples of Sentences

1. A follows B. -- BA
2. B precedes A. -- AB
3. A is followed by B. -- AB
4. B is not followed by A. -- BA
5. B is preceded by A. -- BA
6. A does not precede B. -- BA

TABLE 3

HYDROGEN-OXYGEN DECOMPRESSION SCHEDULE

DEPTH (FSW)	TIME (MIN)	BREATHING MIXTURE
0-100	1	80%He-20%O_2
100-200	1	97%He- 3%O_2
200	113	97%H_2- 3%O_2
200	4	97%He- 3%O_2
200	1	80%He-20%O_2
200-140	1	" "
140	5	" "
130	10	" "
120	15	" "
110	15	" "
100	20	" "
90	20	38%He-33%N_2-29%O_2
80	20	AIR
70	30	65%N_2-35%O_2
60	30	" "
50	30	" "
40	10	AIR
40	60	OXYGEN
40	10	AIR
30	60	OXYGEN
20	10	AIR
20	60	OXYGEN
20	10	AIR
10	60	OXYGEN
10-0	1	"

TOTAL DECOMPRESSION TIME 7 HOURS AND 57 MINUTES.

TABLE 4

HELIUM-OXYGEN DECOMPRESSION SCHEDULES

DEPTH (FSW)	TIME (MIN.) $He-O_2$ SCHED. #1	TIME (MIN.) $He-O_2$ SCHED. #2	BREATHING MIXTURE
0-200	2	2	$80\%He-20\%O_2$
200	113	113	$97\%He-3\%O_2$
200	5	5	$80\%He-20\%O_2$
200-150	1	1	" "
150	10	10	" "
140	10	10	" "
130	10	10	" "
120	10	10	" "
110	10	10	" "
100	20	20	" "
90	20	20	$33\%N_2-38\%He-29\%O_2$
80	20	20	AIR
70	20	20	$65\%N_2-35\%O_2$
60	20	20	" "
50	30	30	" "
40	10	10	AIR
40	60	60	OXYGEN
40	10	10	AIR
30	60	60	OXYGEN
20	10	10	AIR
20	60	60	OXYGEN
20	10	10	AIR
10	75	50	OXYGEN
10-0	1	1	"

TOTAL DECOMPRESSION TIME: SCHEDULE #1, 7 HOURS 57 MINUTES; SCHEDULE #2, 7 HOURS, 32 MINUTES.

TABLE 5

NITROGEN-OXYGEN DECOMPRESSION SCHEDULES

DEPTH (FSW)	BREATHING MIXTURE	TIME (MIN.) N_2-O_2 SCHED. #1	TIME (MIN.) N_2-O_2 SCHED. #2	TIME (MIN.) N_2-O_2 SCHED. #3
0-200	AIR	2	2	2
200	97%N_2- 3%O_2	113	113	113
200	AIR	5	5	5
200-140	"	1	1	1
140	"	5	5	5
130	"	5	5	5
120	"	5	10	10
110	"	5	10	10
100	"	10	15	15
90	"	10	15	15
80	"	15	20	20
70	65%N_2-35%O_2	20	20	20
60	"	20	30	30
50	"	30	45	45
40	AIR	10	10	10
40	OXYGEN	60	60	60
40	AIR	10	10	10
30	OXYGEN	60	60	60
20	AIR	10	10	10
20	OXYGEN	60	60	60
20	AIR	10	10	10
10	OXYGEN	60	75	96
10-0	"	1	1	1

TOTAL TIME (MIN.): SCHED. #1 - 407 SCHED. #2 - 472 SCHED. #3 - 493

TABLE 6

DECOMPRESSION SICKNESS: PROJECT HYDROX II

MIXTURE	DECOMPRESSION SCHEDULES	SUBJECT	BENDS?	RX NEEDED?	RECURRENCE?
N_2-O_2	I	P.G.*	YES	NO	NO
" "	II	P.G.*	YES	NO	NO
" "	II	P.M.	NO	NO	NO
" "	II	P.M.	NO	NO	NO
" "	II	M.E.**	NO	NO	NO
" "	II	M.E.	YES	NO	NO
" "	II	S.A.	YES	YES	NO
" "	III	S.A.	YES	YES	NO
H_2-O_2	I	P.G.	NO	NO	NO
" "	I	P.G.	YES	YES	NO
" "	I	P.M.	NO	NO	NO
" "	I	P.M.	NO	NO	NO
" "	I	M.E.	NO	NO	NO
" "	I	M.E.	YES	YES	NO
" "	I	S.A.	YES	YES	NO
" "	I	S.A.	YES	YES	NO
He-O_2	I	P.G.	NO	NO	NO
" "	I	P.M.	NO	NO	NO
" "	I	M.E.	NO	NO	NO
" "	I	S.A.	NO	NO	NO
" "	II	P.G.	YES	NO	NO
" "	II	P.M.	NO	NO	NO
" "	II	M.E.	YES	NO	NO
" "	II	S.A.	YES	NO	NO

* Symptoms of dizziness and nausea at 200 FSW.

** Symptoms of dizziness, nausea and vomiting at 200 FSW.

TABLE 7

DECOMPRESSION SICKNESS INCIDENCE BY REGIMES

DECOMPRESSION TABLE	NO. DIVES	NO. CLEAN DIVES	NO. BENDS (NO RX)	NO. BENDS REQUIRING RX	TOTAL NO. BENDS
N_2-O_2 (I, II & III)	8	3	3	2	5
H_2-O_2	8	4	0	4	4
He-O_2 (I)	4	4	0	0	0
He-O_2 (II)	4	1	3	0	3
TOTAL	24	12	6	6	12

TABLE 8

PRECENTAGE OF DECOMPRESSION SICKNESS INCIDENCE BY REGIMES

DECOMPRESSION TABLE	NO. DIVES	% CLEAN DIVES	% BENDS (NO RX)	% BENDS REQUIRING RX	TOTAL % BENDS
N_2-O_2 (I, II & III)	8	37.5	37.5	25	62.5
H_2-O_2	8	50	0	50	50
He-O_2 (I)	4	100	0	0	0
He-O_2 (II)	4	25	75	0	75
TOTAL	24	50	25	25	50

TABLE 9

DECOMPRESSION SICKNESS BY SUBJECTS

DIVER	NO. DIVES	NO. CLEAN DIVES	NO. BENDS (NO RX)	NO. BENDS REQUIRING RX	TOTAL NO. BENDS
S.A.	6	1	1	4	5
P.G.	6	2	3	1	4
M.E.	6	3	2	1	3
P.M.	6	6	0	0	0
TOTAL	24	12	6	6	12

TABLE 10

SUBJECT POPULATION VITAL STATISTICS

DIVER	AGE	HEIGHT	WEIGHT	LINEAR DENSITY W/H
S.A.	24	72"	187	2.6
P.G.	24	65"	134	2.06
M.E.	22	69"	145	2.1
P.M.	31	70"	173	2.47
AVERAGE	25.25	69"	159.75	2.32

TABLE 11

MEAN PERCENT CORRECT RESPONSES FOR EACH GAS MIXTURE

MIXTURE	PRE-DIVE		200 FSW		50 FSW		10 FSW	
	$\bar{X}$	σ	$\bar{X}$	σ	$\bar{X}$	σ	$\bar{X}$	σ
HELIOX	61.5	4.26	60.8	3.71	62.3	8.31	57.7	8.45
HYDROX	57.9	4.53	58.6	6.51	58.7	3.39	58.1	4.28
NITROX	58.3	4.49	53.5	4.94	60.1	6.08	57.7	4.05

TABLE 12

SUMMARY OF EXPERIMENTAL DATA
(Results of Sentence Comprehension Tests)

	PERCENT CORRECT				NUMBER ATTEMPTED			
	Pre-Dive	200'	50'	10'	Pre-Dive	200'	50'	10'
Helium								
1	99	99	99	98	62.0	55.5	61.5	54.0
2	96	95	100	99	48.5	54.5	47.0	40.0
3	48	52	51	52	54.0	57.5	47.0	63.0
4	48	56	56	43	39.5	45.0	44.0	50.5
Overall	73	76	77	73	51.0	53.1	49.9	51.9
Hydrogen								
1	99	98	100	100	60.0	58.5	60.0	61.5
2	99	95	96	99	52.0	49.0	45.0	43.5
3	49	54	54	57	60.0	56.0	53.0	50.5
4	39	48	43	44	40.0	42.5	38.5	44.5
Overall	72	74	73	75	53.0	51.5	49.1	50.0
Nitrogen								
1	99	96	100	100	61.5	54.0	64.0	64.0
2	94	95	99	97	48.5	42.0	44.5	48.5
3	55	43	52	50	57.0	51.0	57.0	57.0
4	50	45	45	50	40.0	49.0	44.0	47.5
Overall	75	70	74	74	51.8	49.0	52.4	54.3

TABLE 13

PULMONARY FUNCTION MEASUREMENTS

	PRE-DIVE SURFACE CONTROL ON AIR	200 FT. H_2-O_2	200 FT. He-O_2	200 FT. N_2-O_2	POST-DIVE RECOVERY AIR
1) Forced vital capacity liters	4.57	4.83			4.45
(FVC), % of control	100%	106%	104%	98%	97%
2) Forced expiratory liters	3.82	4.15			3.61
volume in 1 second % (FEV)	100%	109%	97%	85%	95%
3) FEV_2 (liters) in 2 seconds	4.29	4.55			4.14
% of control	100%	106%	101%	87%	97%
4) MVV liters/minute	179	207			178
% of control	100%	116%	88%	46%	99%
5) MEFR liters/second	9.11	10.74			8.67
% of control	100%	118%	95%	42%	95%
6) MIFR liters/second	8.19	9.89			8.30
% of control	100%	121%	73%	48%	101%

Since the number of subjects and data vary for each condition, all data except for pre-dive surface control on air is presented as a mean of each man's percentage of surface control.

TABLE 16

MOLECULAR WEIGHT AND SOLUBILITY FACTOR IN WHOLE BLOOD, WATER AND OLIVE OIL FOR HYDROGEN, HELIUM AND NITROGEN:

GAS	H_2	He	N_2
Molecular weight	2.016	4.003	28.016
M.W.	1.42	2.0	5.29
M.W. Ratio (H_2=1)	1.0	1.409	3.727
Solubility ml/ml at 760 mm Hg 37° C for:			
Water	0.0162	0.0087	0.0127
Whole Blood	0.0149	0.0087	0.0122
Olive Oil	0.0502	0.0150	0.0670
Partition Coefficients at 37 to 38° oil/water	3.1.	1.724	5.275
Relationship	N_2/H_2	N_2/He	H_2/He
Partition Coefficients	1.7	3.06	1.80
Whole Blood and Watery Tissues	0.819	1.402	1.71
Pure Fat as Oil	1.301	4.467	3.43

TABLE 19

N_2+He SURFACING TISSUE TENSIONS FROM H_2-O_2 DIVES
(Using Hypothetical Tissue 1/2 Saturation Times of
300,360,480 & 720 Minutes for N_2 and 150,180 & 240 Minutes for He)

N_2 1/2T Values	300	300	300	360	360	360	480	480	480	720	720	720
He 1/2T Values	150	180	240	150	180	240	150	180	240	150	180	240
P_{N_2} Sched #1	20.1	20.1	20.1	22.5	22.5	22.5	22.9	22.9	22.9	22.8	22.8	22.8
P_{He} Sched #1	16.6	20.3	24.7	16.6	20.3	24.7	16.6	20.3	24.7	16.6	20.3	24.7
P N_2+He	36.7	40.4	44.8	39.1	42.8	47.2	39.5	43.2	47.6	39.4	43.1	47.5
P_{N_2} Sched #2	21.3	21.3	21.3	21.8	21.8	21.8	23.4	23.4	23.4	23.1	23.1	23.1
P_{He} Sched #2	18.7	22.4	26.6	18.7	22.4	26.6	18.7	22.4	26.6	18.7	22.4	26.6
P N_2+He	40.0	43.7	47.9	40.5	44.2	48.4	42.1	45.8	50.0	41.8	45.5	49.7

FIGURE 1

Repetitive Air Dive Profile

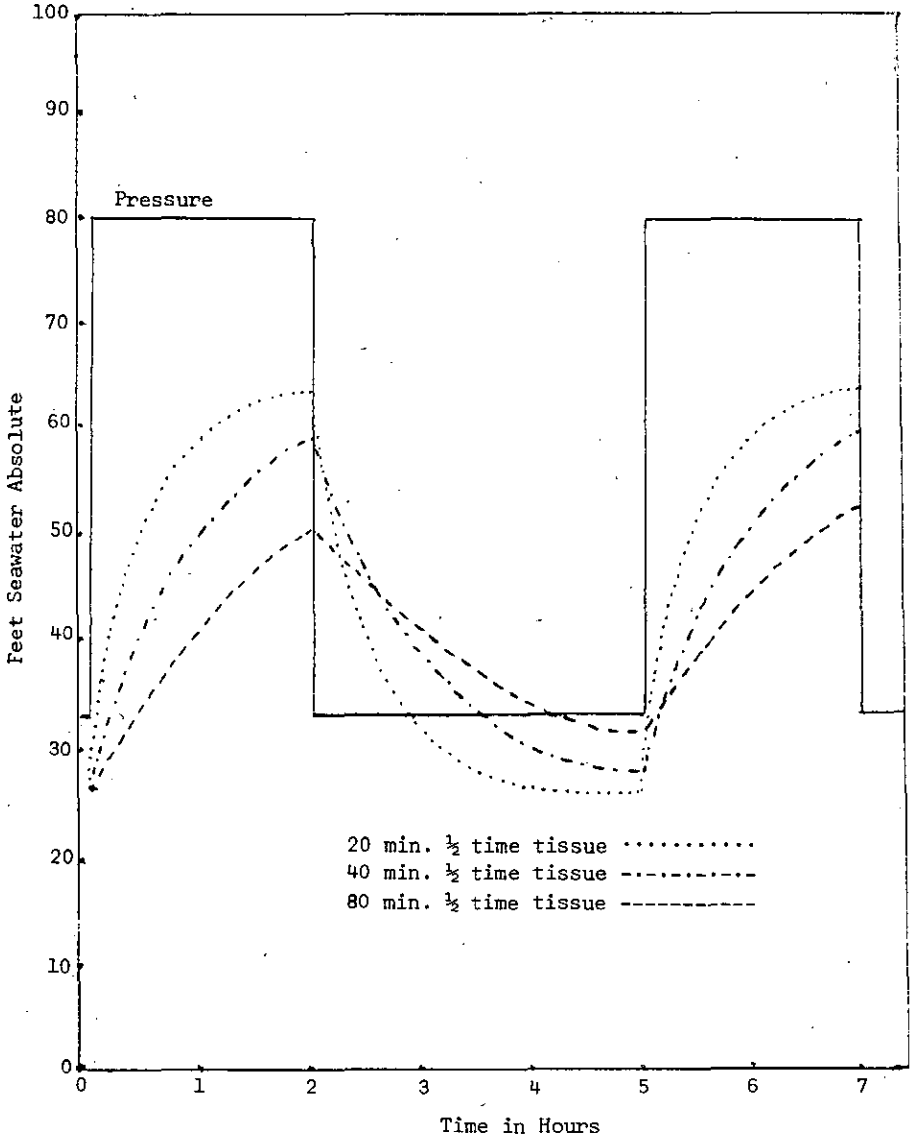


FIGURE 2

Multiple Inert Decompression Schedule

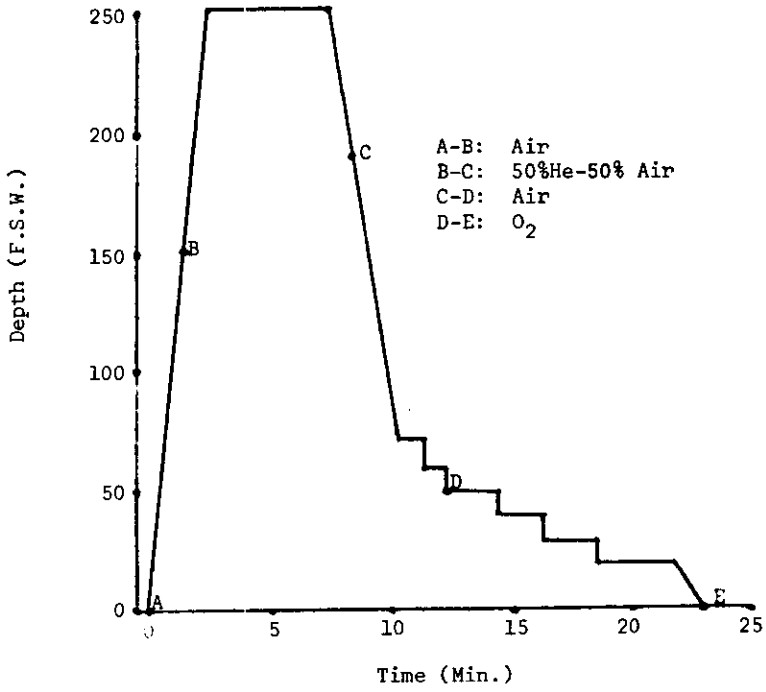


FIGURE 3

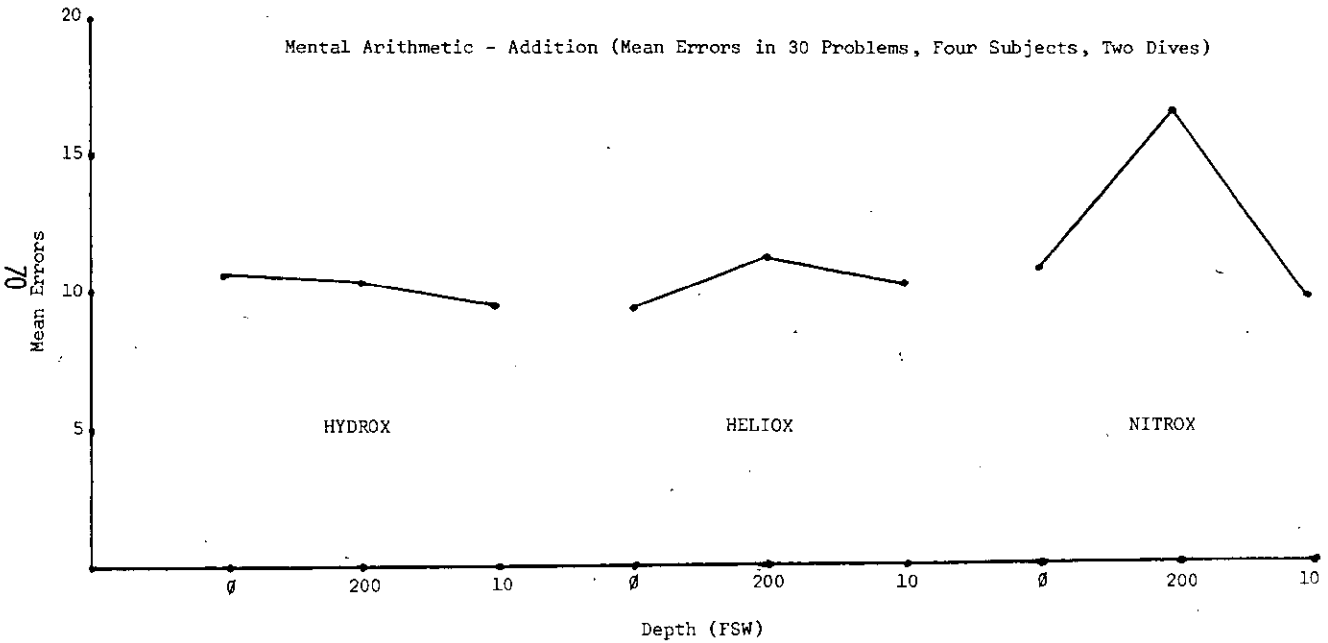

Mental Arithmetic - Addition (Mean Errors in 30 Problems, Four Subjects, Two Dives)
20
15
10
5
% Mean Errors
HYDROX
HELIOX
NITROX
ø
200
10
ø
200
10
ø
200
10
Depth (FSW)

FIGURE 4

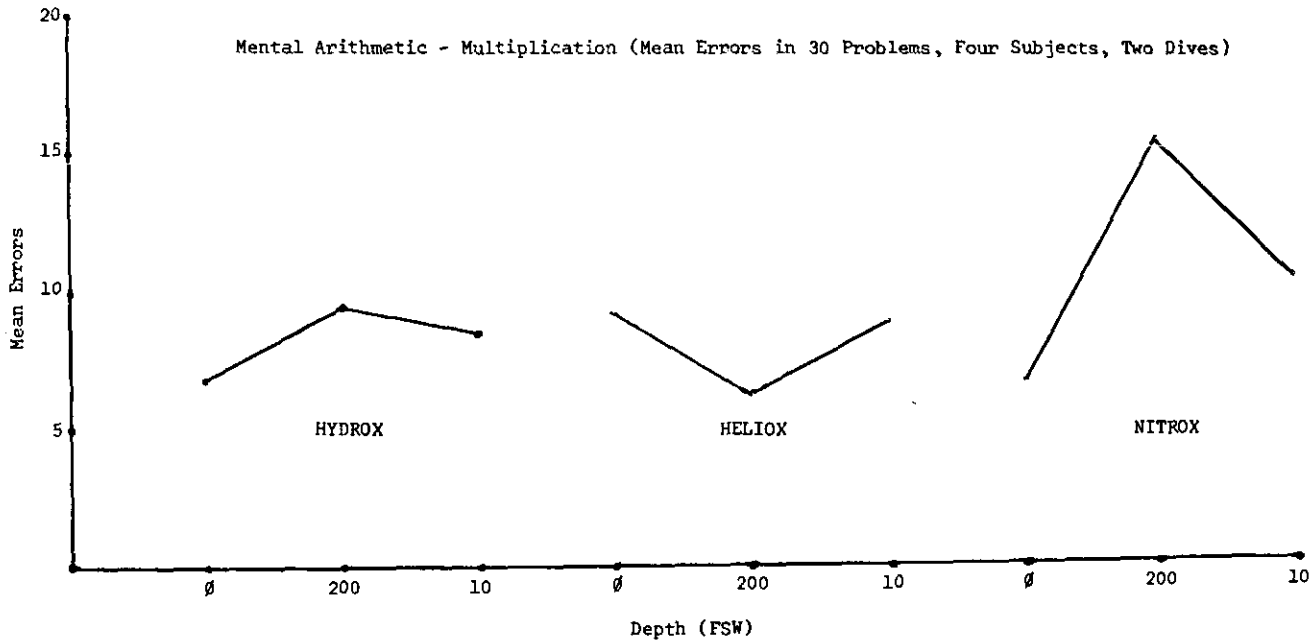

Mental Arithmetic - Multiplication (Mean Errors in 30 Problems, Four Subjects, Two Dives)
Mean Errors
20
15
10
5
HYDROX
HELIOX
NITROX
ø
200
10
ø
200
10
ø
200
10
Depth (FSW)

FIGURE 5

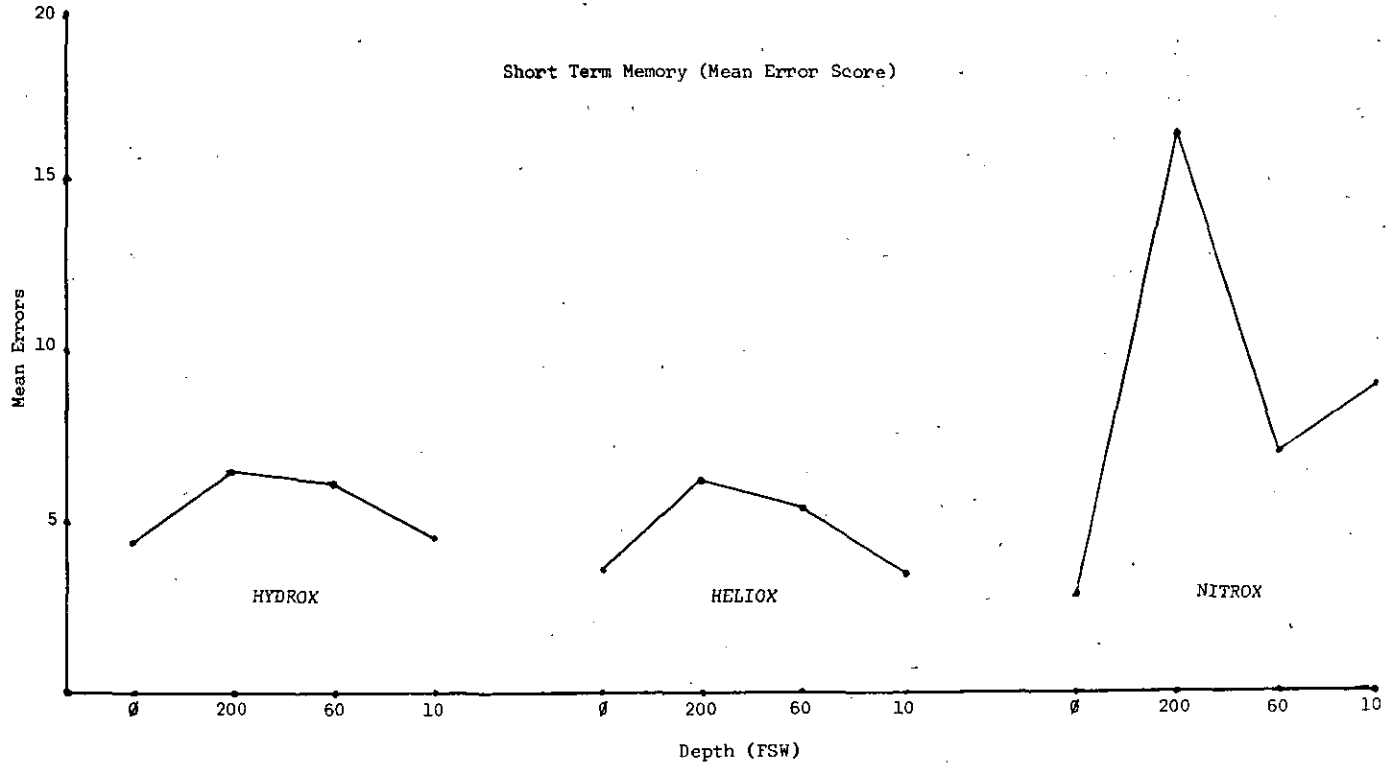

Short Term Memory (Mean Error Score)
Mean Errors
20
15
10
5
HYDROX
HELIOX
NITROX
Ø
200
60
10
Depth (FSW)

FIGURE 6

Signal Detection (Percent Correct Responses)

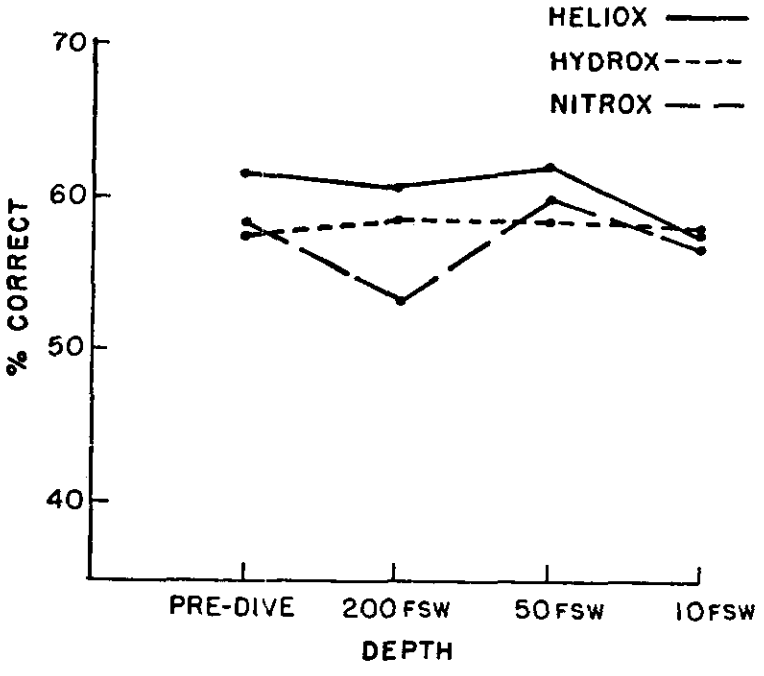
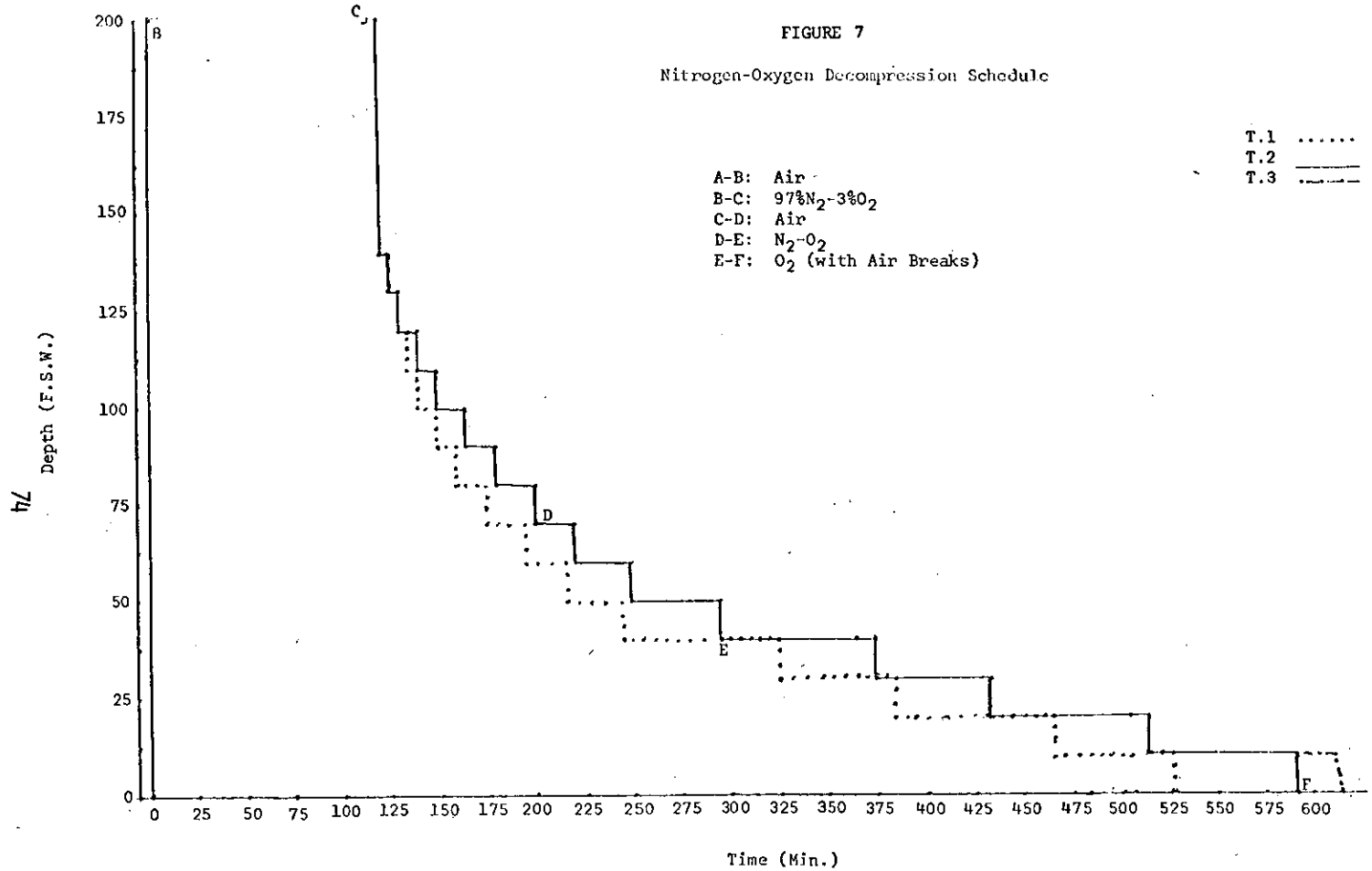


FIGURE 7

Nitrogen-Oxygen Decompression Schedule



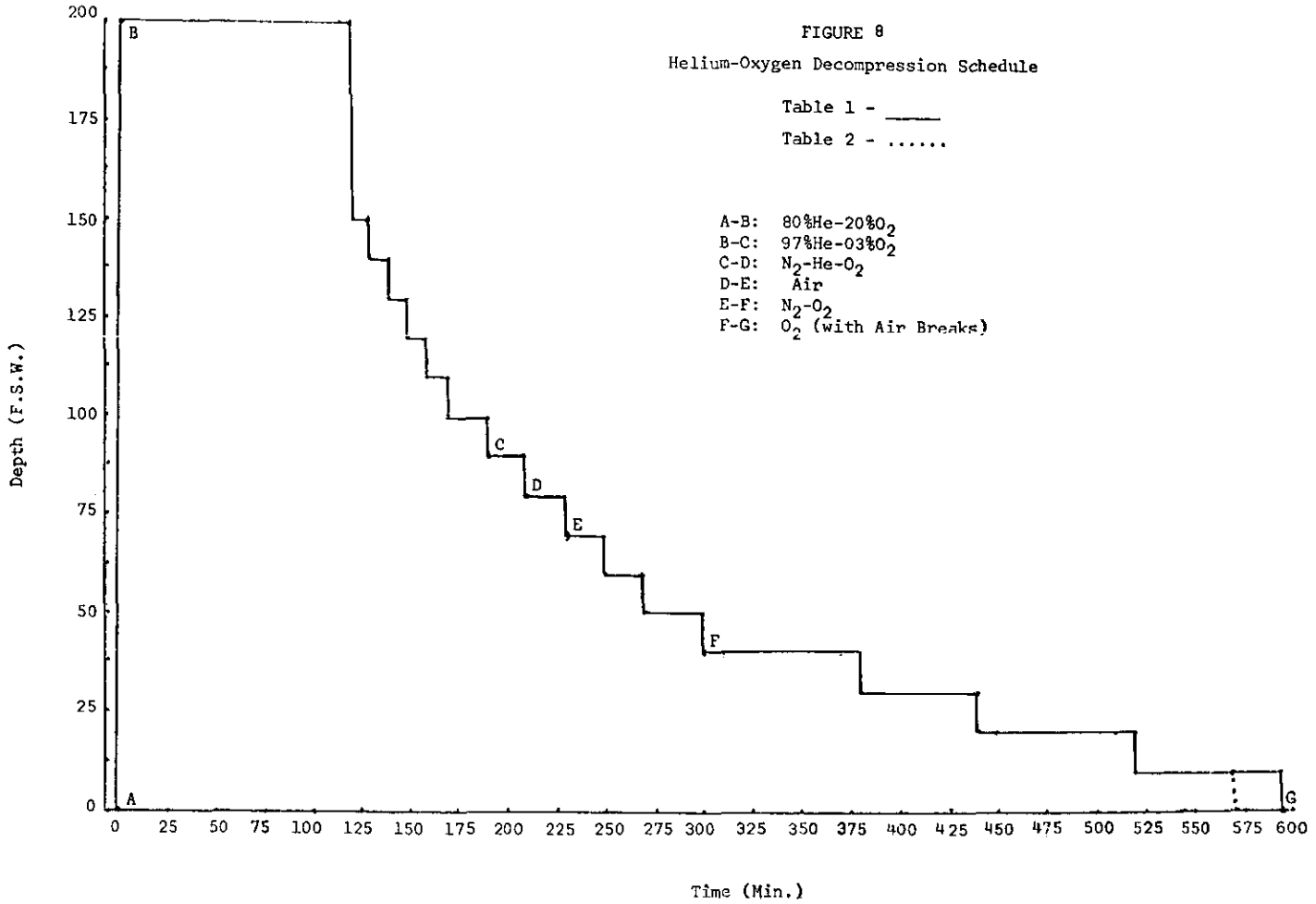


FIGURE 8

Helium-Oxygen Decompression Schedule

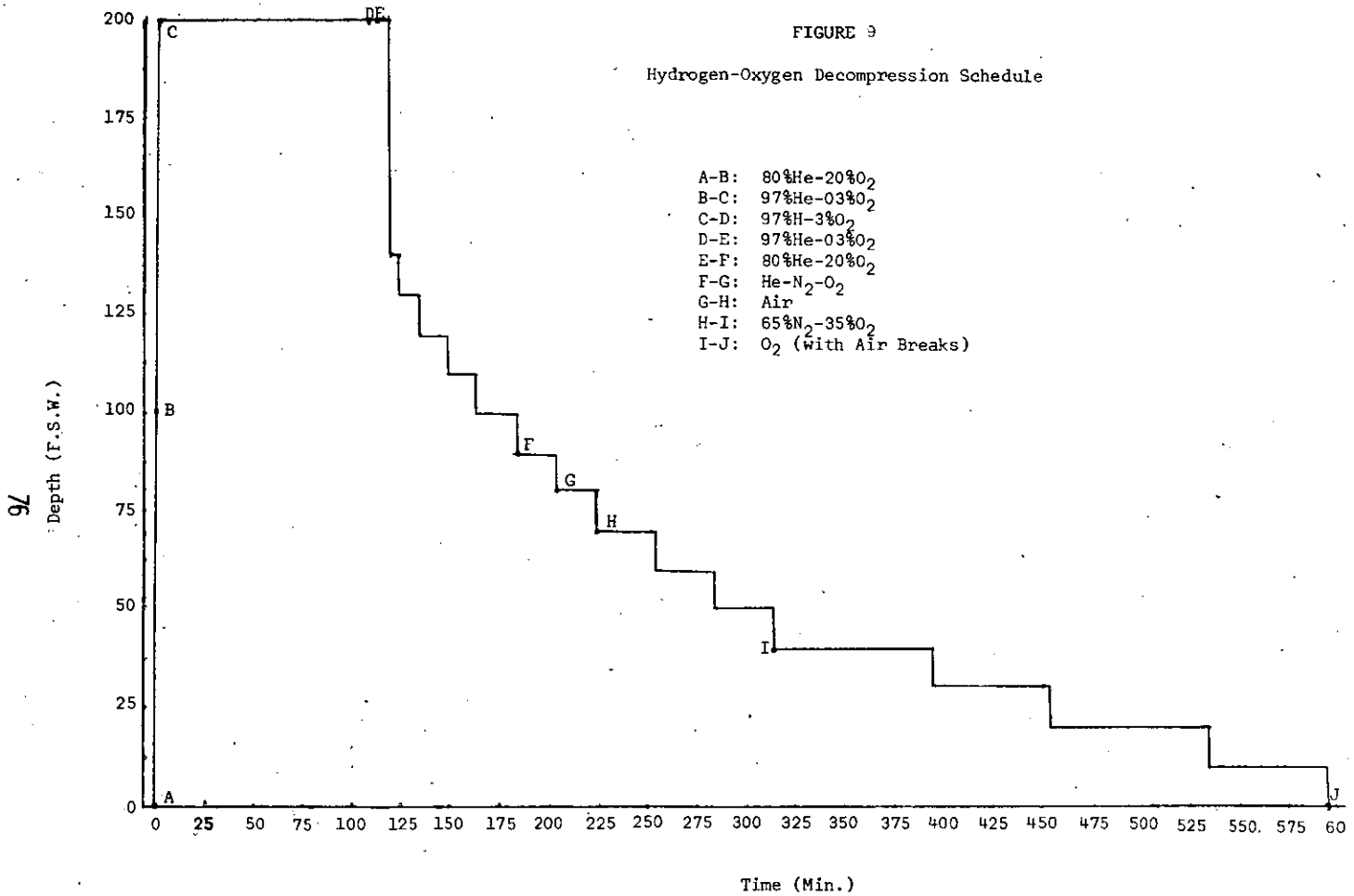
Table 1 - ____

Table 2 - .....

A-B: 80%He-20%O_2
B-C: 97%He-03%O_2
C-D: N_2-He-O_2
D-E: Air
E-F: N_2-O_2
F-G: O_2 (with Air Breaks)

FIGURE 9

Hydrogen-Oxygen Decompression Schedule



Reprinted From
Marine Technology Society
"Working Diver Symposium - 1972"

PRELIMINARY STUDIES OF HYDROGEN-OXYGEN BREATHING MIXTURES FOR DEEP SEA DIVING

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ABSTRACT

Experiments using various mixtures of hydrogen and oxygen were conducted with divers down to 200 feet and dogs down to 1000 feet. No contradictory indications to the use of hydrogen-oxygen as a breathing medium were found; no significant changes resulted from exposure of subjects to this mixture under the conditions tested. It is concluded that there is no significant difference between the diver's speech in hydrogen-oxygen and his speech in helium-oxygen where the oxygen percentage and depth are constant. An unscrambler that would work for helium-oxygen should also work for hydrogen-oxygen. The temperature comfort ranges for the two gas mixtures are also similar. Some difficulty is encountered in assessing the role played by hydrogen in determining decompression requirements. However, similar requirements are evidenced in the decompression requirements of helium-oxygen and hydrogen-oxygen. Hydrogen is seen to possibly be the inert gas of choice for exposures to extreme depths.

INTRODUCTION

Hydrogen is the lightest of all gases and therefore might be expected to offer the lowest possible breathing resistance at the ever increasing depths being considered for future diving operations. On the basis of the solubility and diffusion coefficients of hydrogen as compared with helium and nitrogen, Buhmann[1] suggested that the uptake and elimination rates in body tissue should be more rapid for hydrogen than for nitrogen and less rapid for hydrogen than for helium. On the other hand, Keller[2], believing that the diffusion coefficient alone provided a better indication of inert gas transport limitation, suggested that the uptake and elimination times for hydrogen should be even more rapid than for helium.

In spite of the potential advantages of hydrogen-oxygen as a breathing mixture for very deep diving operations, investigators were discouraged

from experimenting with "Hydrox" in view of the explosive and flammable properties of this mixture over a broad range of hydrogen/oxygen ratios. However, work done by the Bureau of Mines[3] and by Dorr[4] of Ocean Systems has demonstrated that oxygen percentages as high as 3 or 4 percent in hydrogen are completely safe with respect to flammability and explosive hazards. A mixture of 97% hydrogen-3% oxygen could be utilized at depths as shallow as 200 FSW (feet seawater) where the oxygen partial pressure in the mixture would be mathematically equal to the oxygen partial pressure in the air at sea level.

Brauer's[5] work, where mice were exposed to mixtures of oxygen with nitrogen, helium, and hydrogen at elevated pressures indicated that the narcotic potency of hydrogen was less than for nitrogen but greater than for helium. However, convulsive seizures occurred at significantly higher pressures with hydrogen as opposed to helium.

Hydrogen was used briefly as a breathing mixture under pressure by Case and Haldane[6] in 1941. A few years later, Zetterstrom[7] designed a cracking plant for shipboard use to produce a mixture of 72% hydrogen-24% nitrogen-4% oxygen, which was used in a series of dives to a maximum depth of 360 FSW. Mixtures of 96% hydrogen-4% oxygen were used for deeper open-sea dives to a maximum depth of 520 FSW which were reported by Bjurstedt and Severin[8]. The last dive in this series resulted in a diving fatality due to an accident involving the forward winch, which permitted the diver platform to be raised directly to the surface from a depth of 520 FSW without halting for the required decompression stops.

In 1963 Edel[9] developed a system for injecting oxygen directly into hydrogen cylinders at high pressure (2000 psig), and two cylinders were produced by that method containing 97% hydrogen-3% oxygen. In 1967 Edel[10] made two successful dry-chamber dives breathing this mixture for 10 to 20 minutes at a depth of 200 FSW in a single-lock chamber 33 in. in diameter and 8 feet in length. The small size of this chamber permitted very rapid changes in the chamber atmosphere which provided data on atmospheric control for later experiments.

Further manned and animal experiments were conducted in a joint effort between J & J Marine Diving Company and Texas A & M University at the former's facilities at Pasadena, Texas, from September, 1970, to April, 1971, to obtain biomedical data and determine the decompression obligation resulting from longer exposures where body tissue with long half-saturation times would limit or control decompression.

METHODS

Six volunteer subjects (all of whom were divers and had participated in previous hyperbaric experiments) were subjected to the pressure profiles in this series of experiments. The ages of the subjects ranged from 23 to 53 years.

With the exception of the initial two pressure profiles, all tests were made in a double-lock hyperbaric pressure chamber 16 feet long and 4 feet in diameter which had been modified to permit the use of hydrogen-oxygen breathing mixtures.

With the subject in the inner lock, the chamber (initially containing air) was pressurized with pure nitrogen to 200 FSW in two minutes. Upon arrival at 200 FSW, the chamber atmosphere contained approximately 97% nitrogen-3% oxygen, which would be safe with respect to flammability and explosive limits should accidental contamination occur from the hydrogen-oxygen breathing supply. During compression (as shown in Figure 1) the subject would breathe a mixture of 80% helium-20% oxygen for the first minute of compression from surface to 100 FSW and then breathe a mixture of 97% helium-3% oxygen for the final minute of compression from 100 FSW. All breathing mixtures (with the sole exception of hydrogen-oxygen) were supplied from a manifold (located outside the chamber) to the diver via a through-hull fitting to a demand mask located inside the chamber (as shown in Figure 2). The hydrogen-oxygen system was completely separate from the surface-supplied manifold system, with the hydrogen-oxygen mixture supplied from high-pressure cylinders within the chamber to a second demand mask. The Hydrox breathing system included an overboard dump terminating in a flashback arrester outside the building.

Upon arrival at 200 FSW the diver would switch from the surface supply manifold (delivering a 97% helium-3% oxygen breathing mixture) to the hydrogen-oxygen breathing system. In the initial two experiments the subjects remained breathing hydrogen-oxygen throughout their residence at the 200 FSW level. In subsequent exposures the subjects switched to the 97%He-3%O_2 mixture for the final 5 or 10 minutes of the period spent at 200 FSW. With the exception of the initial dive (where the chamber atmosphere was purged during decompression), during the final 5 or 10 minutes at 200 FSW while the subjects were breathing 97%He-3%O_2, the chamber was purged with pure nitrogen to flush out any hydrogen which could have accidentally leaked into the chamber atmosphere. The nitrogen purges were followed by purges with air to increase the oxygen percentage to a level which would provide a respirable atmosphere during decompression should a malfunction occur with the breathing-supply manifold.

In the initial two tests, the diver breathed a mixture of 97%He-3%O_2 during the initial minute of decompression to the first decompression stop and switched to the 80%He-20%O_2 mixture for the second and final minute to the initial decompression stop. In all subsequent tests the subjects switched to an 80%He-20%O_2 mixture during the final minute at the 200 FSW level. The diver ascended to his initial decompression stop on this mixture and remained on the 80%He-20%O_2 mixture during the first portion of his stage decompression.

Oxygen breathing was used (as shown in Table 1) from the 50 or 60 FSW level to surface pressure in Exposures A-E and intermittently with air in Exposures F-I. In the final three experiments of this series with exposure times of 60, 90, and 120 minutes (J, K, & L) at 200 FSW, air, nitrogen-oxygen, and helium-oxygen mixtures were used (in addition to those previously mentioned) to accelerate the rate of elimination of hydrogen and helium from body tissues during decompression and thereby shorten the decompression-time requirements.

In addition, one exposure (see Figure 3) was made in which the subject breathed mixtures of hydrogen-oxygen (97%H_2-3%O_2), helium-oxygen

TABLE 1. PRESSURE PROFILES USED IN PROJECT HYDROX AT 200 FSW

Test	Exposure Time at 200 FSW (min)	Time on H_2-O_2 at 200 FSW (min)	Time on He-O_2 at 200 FSW (min)	Initial Decompression Stop (FSW)	Total Decompression Time (min)	Decompression Sickness Occurrence	Recompression Required?
A	10	10	0	60	30	No	No
B	20	20	0	100	57	Yes	No
C	20	15	5	100	64	No	No
D	30	15	5	100	86	No	No
E	30	10	20*	100	108	No	No
F	45	40	5	120	156	Yes	Yes
G	45	40	5	120	199	Yes	Yes
H	45	40	5	120	198	Yes	No
I	45	0	45	120	198	No	No
J	60	55	5	120	273	No	No
K	90	80	10	140	382	No	No
L	118	108	10	140	467	No	No

*Tri-inert dive: included 10 minutes breathing air.

(97%He-3%O_2), and air alternately for 10-minute periods on each breathing mixture during the 30-minute exposure at the 200 FSW level to obtain tape recordings of the divers' speech (in cooperation with the U. S. Naval Research Laboratory in Groten, Conn.) in these three mixtures for a comparative study.

In 50% of the tests made for this study, pre- and post-dive blood and urine samples were collected to provide biomedical data to indicate the safety of hyperbaric exposures with hydrogen-oxygen breathing mixtures.

In a parallel program to investigate the effects of prolonged exposure with hydrogen-oxygen breathing mixtures, dogs were exposed to a Hydrox breathing medium under pressure for periods lasting from 1 to 2 days. During pressurization with helium, the oxygen percentage was lowered to provide 2-1/2%O_2 (76 mm Hg· PO_2) at 100 FSW. The 33-cubic-foot chamber was then purged at 100 FSW with hydrogen-oxygen, which was then used to pressurize the chamber to the maximum desired pressure.

The initial exposure was 300 FSW for 24 hours with a 10-hour stage decompression pattern based upon information supplied by Dr. R. D. Workman[11] of Taylor Diving and Salvage Co. and Cdr. Elizabeth Reeves[12] of NMRI. The decompression pattern was successful. Pre- and post-dive blood samples were taken and the animal was sacrificed shortly after arrival.

A second dog was exposed to 1000 FSW for 39 hours in a hydrogen-oxygen atmosphere (see Figure 4) following compression at an average rate of 110 feet per hour. During the exposure the temperature was slowly varied while the animal response was observed. Shivering and panting by the animal were taken as the end points to indicate the comfort range. Decompression was programmed at the rate of 2 minutes per foot following an initial pressure reduction of 100 FSW.

RESULTS

Although the initial experiment (Test A) resulted in a successful decompression with no symptoms of decompression sickness occurring as a result of the pressure-reduction profile used, extending the mathematical model to calculate the decompression obligation for a 20-minute exposure time (Test B) was unsuccessful. In Test B, pain occurred in the left elbow within a few minutes after arrival at the 40 FSW decompression stop which underwent spontaneous remission during the time spent at that level. The pain reoccurred shortly after arrival at the 30, 20, 10, and 0 FSW levels but in each case underwent spontaneous remission during the time spent at these levels without any alteration of the preplanned decompression schedule.

The exposure for 20 minutes at 200 FSW was recalculated in accordance with the results of Test B, and the resulting decompression profile allowing additional time at the deeper stops was tested in the following dive (Test C), which produced no symptoms of decompression sickness. The revised mathematical model successfully predicted the decompression requirements for 30-minute exposures at 200 FSW (Tests D & E); however, extending the calculations to 45 minutes at 200 FSW (Test F) resulted in decompression sickness symptoms occurring upon arrival at

the 10 FSW level which required recompression and treatment in accordance with U. S. Navy Table 6. The decompression schedule was revised with additional time at the shallower decompression levels, increasing the overall decompression time from 156 to 199 minutes. The revised schedule (Test G) resulted in decompression sickness occurring shortly after arrival at 10 FSW which also required recompression treatment.

The failure of the additional decompression time at the shallower levels (which would appear to be excessive in light of earlier experiments) to adequately predict the decompression obligation for such an exposure suggested that the symptoms might well have occurred at the deeper levels. The decompression schedule was accordingly revised, eliminating the time spent at the shallower stops and adding time at the deeper decompression stops with a resulting overall decompression time 1 minute less than the previous schedule. The revised table (Test H) resulted in no symptoms of decompression sickness occurring under pressure. Approximately 1 hour after the subject arrived at surface pressure, he experienced mild pain in his left knee which underwent spontaneous remission within a few minutes and hence did not require recompression treatment.

The decompression schedule used in Test H was used following an exposure (Test I) where 97%He-3%O_2 was utilized in place of 97%H_2-3%O_2 during the 45 minutes spent at 200 FSW. No symptoms of decompression sickness occurred as a result of this exposure.

The mathematical model used to calculate the decompression obligation resulting from the exposure in Test H was applied to calculate the decompression profiles in Tests J, K, and L, with exposure times of 60, 90, and 118 minutes at 200 FSW. All dives were successful with no symptoms of decompression sickness resulting from either exposure.

The 10-hour decompression profile following the exposure of the dog to 300 FSW for 24 hours was successful with no observable symptoms of decompression sickness as a result of the table tested. The second dog, which was exposed to 1000 FSW for 39 hours with a programmed decompression schedule of 20 minutes per 10-foot stage following an initial pressure reduction of 100 FSW, resulted in observable bend symptoms upon arrival at the 360 FSW level. As shown in Figure 4, recompression was attempted three times producing complete remission of symptoms on each occasion, only to have the symptoms recur during subsequent attempts at decompression. The final recompression, followed by a gradual change in the rate of decompression to a final rate of 3 minutes per foot was successful in bringing the animal to surface pressure. Although some residual CNS symptoms were observable following the last recompression, the symptoms did not progress in severity during the subsequent decompression, and complete remission of symptoms was noted within 90 days after the animal arrived at surface pressure.

The dog's response was observed at maximum pressure when the chamber temperature was varied. When the temperature was dropped to 85 F, the animal would shiver; when the temperature was increased to 92 F, the dog would pant. From these data, it was concluded that a temperature halfway between these extremes (88-89 F) represented the optimum comfort temperature for the dog.

DISCUSSION

Perhaps the most significant portion of the program was the work done by the biomedical team in their minute examination of an extremely wide range of biochemical properties to assess the biomedical safety of hyperbaric exposures with hydrogen-oxygen mixtures. Although further biomedical studies covering longer and deeper exposures are very much needed, at present we can see no contradictory indications to the use of hydrogen-oxygen as a breathing medium inasmuch as the data showed no significant changes resulting from exposure to this mixture under the conditions tested.

Analysis of the recordings made of the divers' speech by Dr. R. L. Sergent[13] of the Naval Submarine Medical Research Laboratory in Groton, Conn. have resulted in the conclusion that there is no significant difference between the diver's speech in hydrogen-oxygen and the diver's speech in helium-oxygen where the oxygen percentage and depth are held constant. One would therefore expect that an unscrambler which would work successfully for helium-oxygen may very well be equally successful for hydrogen-oxygen.

The temperature comfort range for a dog exposed to a hydrogen-oxygen atmosphere agreed with observations on dogs exposed to helium-oxygen atmospheres at the same pressures and oxygen/inert ratios. The optimum temperature (between 88 and 89 F) was also identical to the temperature found most comfortable in a multiday-excursion dry-chamber dive on helium-oxygen at 620 FSW by Ocean Systems divers as reported by Hamilton et al[14].

In attempting to evaluate the decompression obligation resulting from exposures with hydrogen-oxygen breathing mixtures, some difficulty is encountered in assessing the role played by hydrogen, which is partially obscured by the other inerts used during decompression. Yet, as shown in Table 1 (Exposures H & I), an empirically derived decompression table following a 45-minute exposure on hydrogen-oxygen at 200 FSW was equally satisfactory following the same exposure wherein helium-oxygen was used as a breathing mixture. Although no dives were made in which nitrogen-oxygen was used as a breathing mixture in a comparable exposure, reference to the U. S. Navy Diving Manual[15] (extreme exposure tables for air) shows that decompression tables in which the H_2 partial pressure is approximately equal to the H_2 partial pressure used in their experiments are quite dissimilar from the empirically derived hydrogen-oxygen tables.

A comparison of the U. S. Navy helium-oxygen and air tables reveals the requirement for much deeper initial decompression stops when helium is used as compared with air. Reference to Table 1 shows this requirement to apply for hydrogen-oxygen exposures as well. Apparently, the decompression requirements following hydrogen-oxygen exposures are somewhat similar to the decompression requirements following a comparable exposure with helium-oxygen, and they are quite dissimilar to the decompression requirements following a comparable nitrogen-oxygen exposure.

Analysis of present data indicates hydrogen-oxygen to be potentially comparable with or superior to helium-oxygen for deep-diving operations and suggests the possibility that hydrogen may be the inert gas of choice for exposures to extreme depths.

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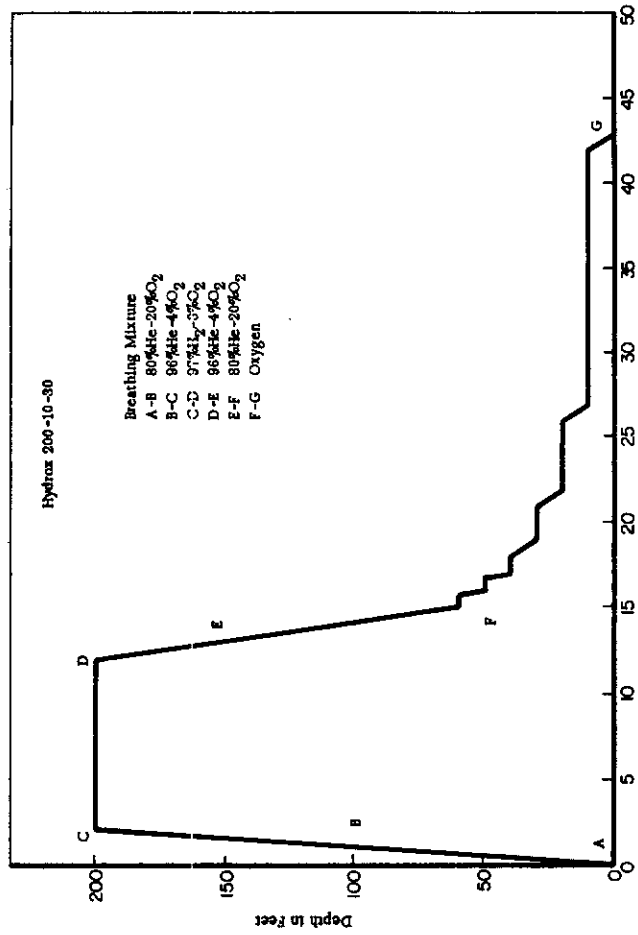

FIGURE 1. MANNED EXPOSURE BREATHING HYDROGEN-OXYGEN FOR 10 MINUTES AT 200 FSW

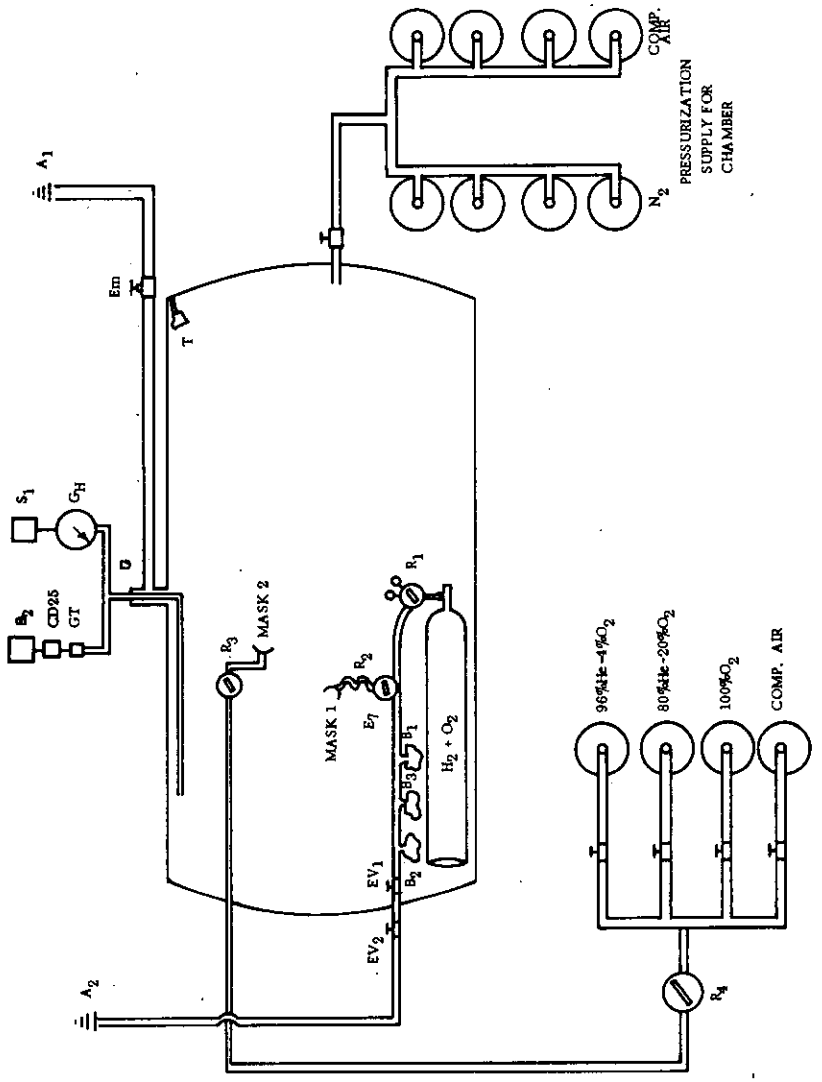

FIGURE 2. DIAGRAM OF TEST FACILITY FOR MANNED HYDROGEN-OXYGEN EXPOSURES

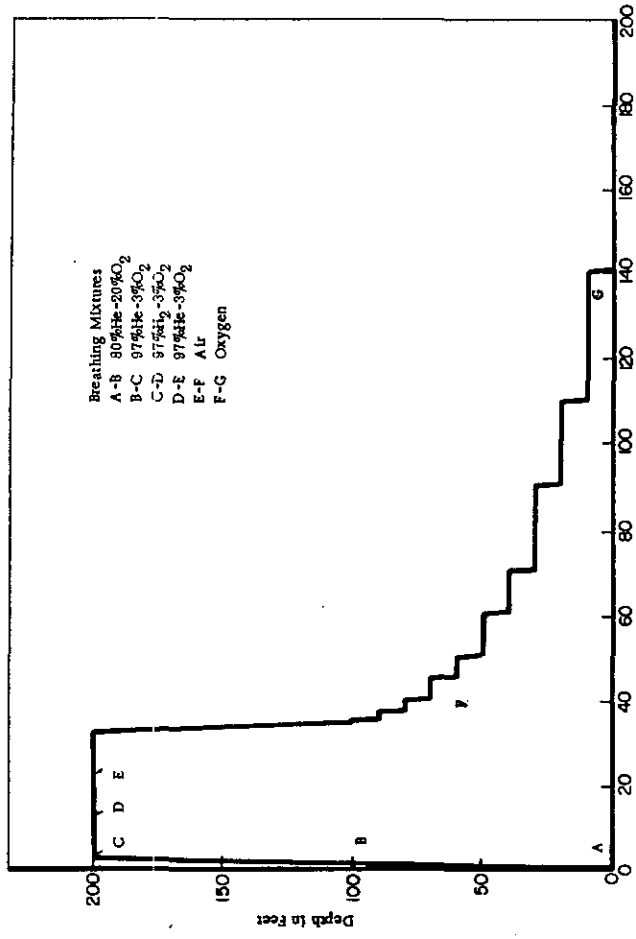

FIGURE 3. TRI-INERT DIVE AT 200 FSW

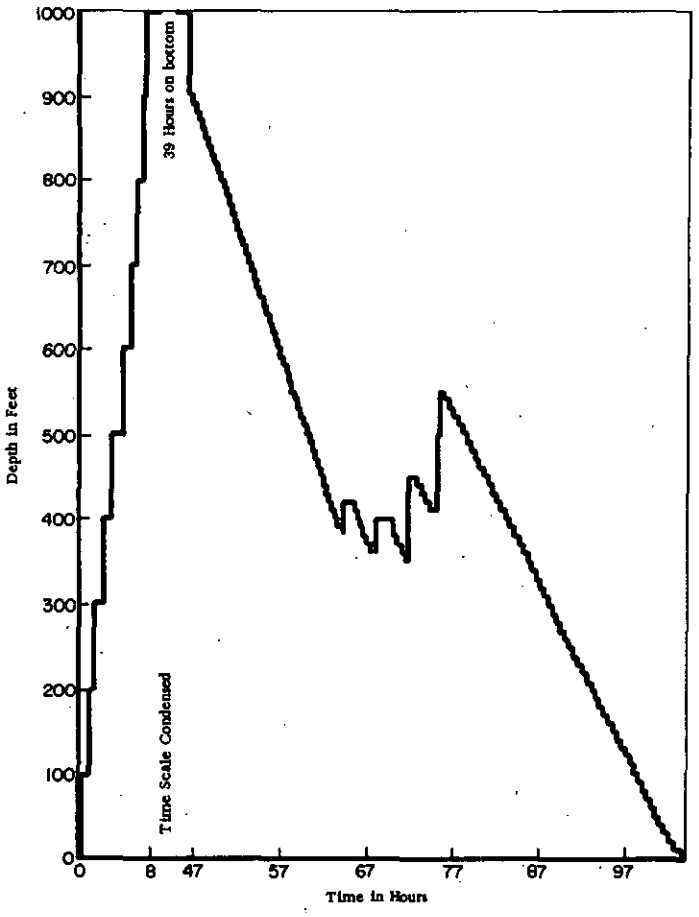

FIGURE 4. HYDROGEN-OXYGEN DOG EXPOSURE TO 1000 FEET

Q. I've heard that there is a possibility of hydrogen solidification of fat in animals by hydrogenization. Any comment on that? And a related question on this – at what pressure does the hydrogenization of fat to margarine occur?

A. Well, I don't know with respect to margarine, but we wondered about this problem, too, and thanks to the work of the biomedical team, I think we are able to say that there was no change in, for example, cholesterol from the pre- to post-dive exposures regardless of the time. Either in the human exposures to 2 hours at 200 feet or animal exposures to 1000 feet for 39 hours. We could detect no significant change.

Q. Here are two more related questions. What is the flammability range of oxygen in hydrogen and what are the explosive oxygen-helium ratios you identified?

A. The explosive ratios referred to were all with hydrogen-oxygen. The explosive range varies with temperature and pressure, but I think it varies generally from about somewhere above 5 percent – I think 6 percent – to about 9 percent oxygen in hydrogen. This explosive and flammability range is lower, and I believe that can get down to something like 4.2 percent for the right pressure-temperature conditions. I'm not quite sure exactly what that is, but I remember we went at least 1 percent beyond the worst condition.

Q. What indicators of decompression illness were used in the dog trials?

A. The dog's reaction during decompression. Now, of course, one problem that we have with dogs is that they can't communicate with us quite as well as the divers. Of course, if you could hear some of the hydrogen-oxygen speech that we had you might question that statement a bit. But they will communicate inadvertently without meaning to; for example, if a bubble occurred in the hind limb of an animal he would favor that limb and, even though there was no reason for suspecting decompression sickness, we would periodically make the dog get up and walk around to see if we could observe a limp; if we observed the animal limping, we concluded that he had decompression sickness. Now, obviously, this probably was precipitated at some deeper stop, where if it had been a human being he could have communicated and said "I've got a bubble", but unfortunately we can only use objective symptoms with the dogs.

Q. Have there been accidents or fatalities involving hydrogen breathing mixtures?

A. The only fatality recorded was the one that involved Zedestrom, the man who started this all, really, in Sweden. I have heard something about an explosion in mixing somewhere, but I don't know whether or not this is really true; when we are looking at mixing we are

looking at the most dangerous portion of the problem. However, now we have found that we can get a commercial company to supply us with mixtures in as large a quantity as we desire. I think they feel that they've solved this particular problem.

Q. Under what circumstances will hydrogen-oxygen diving compare with helium-oxygen diving in cost efficiency? And a related question – could hydrogen-oxygen mixture have any potential value at depths where helium is now used?

A. Cost efficiency is very difficult to determine as yet. We are just starting and we have a great deal to learn about the requirements. But potentially, cost efficiency should be better for hydrogen-oxygen than it would be for helium-oxygen because helium-oxygen costs quite a bit; with hydrogen-oxygen, what they are really charging for is the mixing process; as volume goes up, this cost will come down, and the indications are that it will eventually be lower than helium, assuming that helium does not rise in cost. And I think there are indications that helium may rise in cost over the next 20 years; I think there are very strong indications that this may be true. There are some advantages in cost and in solving operational problems in the same depth range that helium-oxygen is used now. Of course, right now I am referring to dives made from the United States in the Gulf of Mexico and off the East and West Coasts. When you go overseas, the problem is magnified and the relative cost efficiency becomes better for hydrogen, because it costs an arm and a leg to get helium over there. I hear price is about $100 a bottle overseas in some locations, and when you compare this with a potential cost of $15 a bottle for hydrogen-oxygen, this starts to become attractive on a cost basis.

Q. What difficulties might be expected from the use of hydrox in actual commercial military dives?

A. Well, I think with respect to the explosive limits, we get the worst problem in the mixing, which apparently has been solved satisfactorily. The next worst condition is working in a dry chamber with an animal, because then we have to flood the entire chamber with the hydrogen-oxygen mixture and this is a bit difficult to do correctly and you only get one chance at these things, unfortunately; and we haven't been able to train the dogs to use masks. With divers we've had a little better success in that direction. The divers can breathe from the masks and the exhalation can be dumped overboard and this makes it that much safer. But, still, no matter how remote, there's still a very tiny possibility that there could be some contamination. This is the reason why we purge with nitrogen following a dive. But when you get down to the open sea, all the problems are gone, practically, because the diver is never breathing hydrogen-oxygen at a depth of less than 200 feet and, if he is on open circuit which is economical with hydrogen-oxygen, he is dumping it directly into the water and it's gone. This is the best of all operating conditions with hydrogen-oxygen, which is quite the reverse from the conventional diving problem.

THE INTENSITY OF THE NARCOTIC ACTION OF HYDROGEN AT HIGH PRESSURE

by

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Translated from
Farmakologiya i Toksikologiya, 6, (1943), 29-32

by

E.R. Hope

Defence Scientific Information Service
DRB Canada
October 1969

T 532 R

69-850

Translated from Farmakoligiya i Toksikologiya, 6, (1943), 29-32.

THE INTENSITY OF THE NARCOTIC ACTION OF HYDROGEN AT HIGH PRESSURE

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In my book on the biological activities of gases under pressure (1941) I gave theoretical grounds for the expectation that any so-called "physiologically indifferent" gas would have, under high pressure, a narcotic action. Experiments were described that supported this expectation and showed it to be possible to produce nitrogen, argon and crypton narcosis in some vertebrate and invertebrate animals, including white mice. The fact that the said narcosis in an atmosphere of each of these gases is observed at quite different pressures negates any hypothesis of a mechanical narcosis – that is, any assumption that the observed completely reversible paralysis is the result of a purely mechanical effect of high pressure.

Acting less strongly than the other gases studied was the gas of minimal molecular weight, neon. And more particularly, helium. A mouse was still far from being narcotized even at 100 atmospheres pressure (of which 96 atmospheres represented helium partial pressure).

+++++++

Hitherto, research on the action of hydrogen under pressure has been quite neglected. This lightest of all known gases should theoretically be also the gas with the weakest narcotic properties. Of course, its solubility in water is nearly twice that of helium; the coefficients of solubility of these gases in water (in round figures) are: $\lambda(H_2)$ at 40°C, 0.019; λ(He) at 40°C, 0.011. This should somewhat increase the narcotic action of hydrogen, but still it is to be expected that this gas will act no more strongly than helium.

It would be not only of theoretical but also of considerable practical interest if this understanding of the matter were confirmed. In my above-mentioned monograph I described a "method of cycled or alternating administration of gases" as a means – most radical in principle – of preventing decompression sicknesses subsequent to work under high pressures. But for the application of this method at very high pressures it is necessary to have at least two gases capable of serving in turn as "oxygen diluents" and at the same time exerting a minimum of narcotic effect. One such gas is helium. In spite of major defects (danger of explosion), hydrogen is the most likely partner for helium, in view of its expected feeble narcotic properties.

Is hydrogen in fact only a feeble narcotic?

To clear up this question, I have as yet been able to mount only two preliminary experiments. The principal hindrance to this research was that large quantities of pure electrolytic hydrogen were not available to me. I had to work with technological hydrogen containing a number of impurities, including 0.1 per cent of oxygen, 0.1 per cent of carbon dioxide, 0.3 per cent of carbon monoxide and 1 per cent of nitrogen.

At my request, engineer N.T. Prokof'yev designed special absorbers for clearing impurities out of gases at high pressures (up to 100 or 120 atmospheres). The first of these absorbers was, in the experiments described below, intended to remove the main toxic impurity of the hydrogen, namely carbon monoxide. It was filled with an ammoniacal solution of cuprous chloride (Cu_2Cl_2); the ammonia was retained by a concentrated aqueous solution of zinc chloride. But the course of events (the tests were set up in June of 1941) gave us no chance to

determine the optimum conditions for the absorption of carbon monoxide; the research was broken off after the first preliminary experiments. In these experiments we did not succeed in completely freeing the gas of carbon monoxide; consequently at high pressure a toxic concentration of carbon monoxide was formed, which in fact caused grave or even lethal intoxication of a white mouse placed in the pressure chamber. Yet in view of the fact that in the international scientific literature there is a lack of data on the action of hydrogen at high pressures (of the order of some tens of atmospheres) even these very imperfect but nevertheless unique experiments take on a certain interest and even provide some material for answering the question which we set ourselves. Let us give, for example, extracts from the record of one such experiment.

Experiment no. 212 of 10 June 1941.

A white mouse of weight 25 g was placed in the pressure chamber.

At 17:55, pressure chamber closed. At 17:57 we commenced to feed a mixture of 95 per cent nitrogen and 5 per cent oxygen; pressure after one minute brought to five relative (six absolute) atmospheres. At 18:00 hydrogen feed commenced. Nothing particular noted in the behaviour of the mouse.

At 18:05 the total relative pressure (hereinafter too we shall be citing *relative* pressures) was 15 atmospheres, with 10 atmospheres of this representing hydrogen. The mouse sat quietly in its place; only a deeper respiration than usual was observed.

By 18:14 the pressure had been carried to 25 atm with 20 atm of this being hydrogen. The mouse was plainly sluggish; respiration became infrequent and deep. When the whole pressure chamber was shaken the mouse moved slowly from one place to another.

By 18:17 the pressure had reached 30 atm (25 atm H_2), and by 18:20 it was at 35 atm (30 atm hydrogen). The mouse was still in a sitting attitude. At 18:22, after further increase of pressure, the animal was in a semi-recumbent position; more or less spasms observable.

At 18:24, pressure 40 atm, of which 35 atm represented hydrogen. Mouse lying on its side, at times making attempts to stand. Respiration very infrequent.

To test the hypothesis that the observed picture is explainable by carbon monoxide poisoning of the animal, we increased the oxygen partial pressure. For this purpose we fed into the chamber a mixture of 95 per cent nitrogen + 5 per cent oxygen.

At 18:26 the pressure reached 45 atm, with 35 atm of this representing hydrogen. The general condition of the mouse improved. It assumed a half-sitting pose. Also the respiration increased, now attaining 70 per minute.

At 18:28 hydrogen was again fed into the pressure chamber. At 18:29 pressure 50 atm (40 atm hydrogen).

At 18:31, mouse in sitting position. Respiration 84 per minute.

By 18:33 the pressure had been brought to 55 atm (45 atm hydrogen). At 18:34, respiration 86 per minute. Mouse in sitting position.

A mixture of 95 per cent nitrogen and 5 per cent oxygen again fed into the pressure chamber.

By 18:36, pressure 60 atm (with approximately 45 atm hydrogen, 14.25 atm nitrogen and 0.75 atm oxygen). Respiration 82 per minute. Mouse lay on its side and did not get up when the chamber was shaken.

Hydrogen again fed into the pressure chamber.

By 18:41, pressure 65 atm (50 atm hydrogen).

At 18:44, respiration 72 per minute.

By 18:46, pressure 70 atm, hydrogen partial pressure 55 atm.

At 18:47 nitrogen-oxygen mixture fed into the chamber.

At 18:48, pressure 75 atm (around 55 atm hydrogen, 1 atm oxygen, 19 atm nitrogen).

At 18:49, respiration 23 per minute, irregular, arrthythmic.

At 18:50 pressure again increased by introducing into the pressure chamber a nitrogen-oxygen mixture of the same composition as before. *Pressure raised to 80 atms* (55 atm hydrogen, about 1.25 atm oxygen, 23.75 atm nitrogen). Almost complete arrest of breathing; only from time to time isolated deep inspirations.

At 18:52, nitrogen-oxygen mixture again fed into the pressure chamber.

By 18:53, pressure 85 atm (partial pressures: 55 atm hydrogen, 1.5 atm oxygen, 28.5 atm nitrogen).

By 18:55 the state of the mouse had clearly improved: respiration had accelerated to 13 per minute and had become more regular and rhythmic.

At 18:56, respiration 37 per minute.

At 18:57, we again commenced to feed into the pressure chamber a mixture of 95 per cent nitrogen and 5 per cent oxygen.

At 18:58, pressure 90 atm (55 atm hydrogen, 1.75 atm oxygen, 33.25 atm nitrogen).

At 19:00, respiration 8 per minute.

At 19:01, we commenced decompression, and by 19:05 the pressure had dropped to 65 atm. Further decompression was arranged in such a way that the release of the gaseous mixture from the chamber took place with the inlet valve for the nitrogen-oxygen mixture [still] slightly open. In this way we carried out a gradual replacement of the gases in the pressure chamber by a mixture of 95 per cent nitrogen and 5 per cent oxygen.

By 19:10, pressure 45 atm. Outlet valve was closed, but because of a technical error which was not immediately discovered, the [inlet] valve from the nitrogen-oxygen container remained open. Consequently by 19:13 minutes the pressure had again reached 80 atm. Condition of the mouse very grave. Only isolated respiratory movements noticeable. Decompression recommenced.

By 19:24, pressure reduced to 30 atm; by 19:35, to 20 atm; by 19:39, to 12 atm.

At 19:43, pressure 12 atm. The mouse lay motionless as before; did not react to shaking of the pressure chamber. Respiration 23 per minute.

By 19:55, pressure reduced to 3 atm. Respiration, gradually improving, reached 51 per minute.

By 20 hrs the relative pressure had been reduced to 0 atm.

At 20.04 the lid of the pressure chamber was unscrewed. The mouse was taken out of the chamber: by the time it was removed it was again sitting up. Upon being placed on its side, it got up with difficulty, but reacted with saltation to a painful stimulus (strong pressure on tail).

At 20:12 the animal was still sluggish. Observations terminated. Subsequently the mouse showed no signs of illness.

Result of the test: The narcotic action of hydrogen is undoubtedly very feeble. In any case, hydrogen acts much more feebly than nitrogen. It has been shown by many researches, including the particularly detailed studies of T.A. Shtessel' (1937, 1938), that the action of narcotic substances is usually quite rigorously additive. In the mouse, nitrogen produces narcosis at approximately 30-35 atmospheres. Nevertheless, narcosis had not yet occurred at 55 atmospheres pressure of a nitrogen-hydrogen mixture, of which, in round figures, 10 atm was nitrogen partial pressure and 45 atm hydrogen partial pressure. If we take it that here too the narcotic action is additive, then it follows that 45 atm of hydrogen act more weakly than the 20-25 atm of nitrogen that were lacking to bring the experiment up to the narcotic partial pressure of that gas. Consequently it may be expected that narcosis, in the mouse, will be evoked by partial pressures of hydrogen above 70-70 atm (the hydrogen thus acting less than half as strongly as nitrogen).

Actually, the narcotic partial pressures of hydrogen are even higher. In fact we did not observe narcosis occurring as a result of breathing the nitrogen-hydrogen mixture. It is clear that the laterally recumbent position of the animal, the strong inhibition of respiration, and so forth, are explained by carbon monoxide poisoning.

In spite of an accompanying strong increase of the nitrogen partial pressure the condition of the animal was quickly improved by increasing the oxygen partial pressure (introduction of a mixture of 95 per cent nitrogen and 5 per cent oxygen); so much so that the animal even rose out of the recumbent position; even when the intoxication led to an almost complete arrest of respiration, increase of the pressure by introduction of the nitrogen-oxygen mixture was immediately followed by resumption of respiration and its becoming even and rhythmic.

The animal stayed alive even at total pressure 90 atm, with the hydrogen partial pressure at 55 atm.

Evidently the presence of hydrogen made very little change in the toxicity of a gaseous mixture that already contained a narcotic concentration of nitrogen and a highly toxic concentration of carbon monoxide.

It may be confidently affirmed that *the narcotic partial pressures of hydrogen are very high*; they are at least of the same order as for helium.

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Attachment to: 00-E 324/20057-74

PHYSIOLOGY REPORT

N° 01/73/ G.E.R.S.

FINDINGS FROM AN ANIMAL EXPERIMENT ON DIVES USING HYDROGEN-OXYGEN BLENDS

BY

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(UNCLASSIFIED)

Toulon, 18 June 1973

NAVY CINC MEDITERRANEAN AND
MARITIME PREFECTURE
FOR THE 3RD REGION

UNDERWATER STUDY AND
RESEARCH GROUP

N° 40/STUDIES/GERS

From: Capt. Berry
Commanding Officer
G.E.R.S.

To: The Minister of State for
National Defense (NAVY)

Subject: Findings from an Animal Experiment on Dives Using Blends of Oxygen and Hydrogen.

Encl.: A report on the Studies.

It is my privilege to send to you herewith a study report, n° 01/73/GERS, which sums up the findings of an experiment with laboratory animals using mixtures of hydrogen and oxygen, which was condicted at G.E.R.S. from November 1968 to the present.

This text was presented in summary form at Stockholm on 13 June 1973 at the first annual scientific meeting of the European Underseas Biomedical Society.

(Signed) H. Berry

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The limitations on the use of compressed air for diving are well known, and have naturally led researchers to experiment with synthetic breathing mixtures, in which the nitrogen would be replaced with a lighter gas, such as helium or hydrogen, either inert or believed to be so, in an attempt to push back those limitations. In the event, helium made it possible to push back the narcosis threshold, and to push back the limits of the respiratory dynamic constraints, and men (Physalie VI, conducted by COMEX) or animals have since been able to reach considerable depths.

But there are already numerous projects, including those of CHOUTEAU et al. (35,36,37,38,39,40,41,42, 43, 44,45,46,47,48,49, 70), our own (25,56,57,58,83,85,91,93), which can give us an idea of the extreme depth feasible with helium-based mixtures. This limit apparently depends primarily on the SNHP factor described by Brauer, Fructus, and Naquet (21,62,63,64,65,66,96, 98), which must be distinguished from narcosis, and upon the respiratory dynamic constraints, which according to Varene (80, 81, 104,105, 106, 107) and Broussolle (26,27,30,31) would constitute a specific limit on the depth to which man can dive with muscular exertion at around 600 or 700 meters.

Hydrogen, whose molecular weight is half that of helium, looks advantageous from this point of view, and that explains why several research laboratories have recently displayed a revived interest in it, after dumping it around 1948 in view of the progress made in helium-based mixtures for diving, and in view of the dangers of handling hydrogen.

Beginning in November 1968, the Navy's Underwater Study and Research Group, in close collaboration with several university research laboratories in Brest and Marseille, has conducted a series of experiments on the biological effects of hydrogen-oxygen mixtures on animals.

In October 1968, R.W. Brauer tried to conduct here in France, with the help of the COMEX team (X. Fructus and R. Naquet in particular), an experiment in human sea diving with hydrogen-oxygen breathing mixtures. This interesting experiment, HYDRA I, was the culmination of a whole series of experiments with animals done in the United States by Brauer. It called for two divers to breathe a helium-oxygen and a hydrogen-oxygen mixture alternately, at a depth of 300 meters below the sea surface. The experiment was never completed, owing to a number of accidents, the main one of which was the divers' shortness of breath, which prevented either of them from breathing the hydrogen-oxygen mixture.

We have been thinking for several years that there is no proof that hydrogen can be assimilated to an inert gas, and so it seemed to us that a prolonged experiment with the hydrogen-oxygen mixture on animals, under conditions of security, was needed to clear

up this point. At the urging of Capt Leboucher, who was the commanding officer of the GESR at the time, we undertook the experiment reported herein.

But before we present our work, we think it advisable to run through a review -- brief but also as complete as possible -- of the experimental work done in other laboratories on the use of hydrogen-based breathing mixtures.

One short chapter will refresh our memories as to what we know about hydrogen and the dangers involved in handling it.

1. MEMO ON ANIMAL AND HUMAN EXPERIMENTS WITH HYDROGEN DONE ELSEWHERE THAN IN THE G.E.R.S.

1.1. In 1789, Antoine Laurent Lavoisier first replaced nitrogen with hydrogen in a synthetic breathing mixture which he administered to guinea pigs at atmospheric pressure. In his "First Note on the Respiration of Mixtures," he describes his first tests: "We tried to introduce guinea pigs under glass bells filled with a life-supporting mixture and with pure hydrogen, in roughly the proportions by volume as exist between life-supporting air and nitrogen gas in the air of the atmosphere. They remained there quite some time without apparent discomfort, and did not begin to show signs of discomfort until after a lapse of 8 to 10 hours. There seemed to be no diminution in the amount of hydrogen, and just about as much came out of their lungs as had gone in." (77)

It was not until a century and a half later that the oxygen-hydrogen breathing mixture was used again.

1.2. In 1941, Case and Haldane tested a breathing mixture containing hydrogen in brief human dives (33),

1.3. In 1943, N.V. Lazarev published the results of experiments run in earlier years on white mice to determine the narcotic effects of hydrogen. The methodology is quite vague. Lazarev used hyperoxic ternary N_2 H_2 O_2 mixtures, but noted no pathogenic effects other than narcotic effects (78).

1.4. In 1945, Yngve Zotterman conducted several experiments on cats, preliminary to the Zetterstrom human experiments (112,15): dives at 16 atm followed by decompression, apparently without any disturbance. We have no further details about these experiments (duration, makeup of breathing mixtures, physiological parameters studied: in sum, the procedure). Zotterman reports only that the cat was decompressed with no apparent ill effects.

1.5. In 1943, Arne Zetterstrom began his famous string of sea dives (112) with hydrogen. The first were two dives, to 40 and 110 meters. off the "Delos." During these short dives (the second lasted only 15 minutes) Zetterstrom breathed a ternary blend

(4 percent O_2, 24 percent N_2, and 72 percent H_2), without experiencing the slightest discomfort either during or after the dive. Zetterstrom reported that respiratory resistance was considerably lower than those encountered with oxygen-nitrogen or oxygen-nitrogen-helium mixtures.

In 1945, he made two dives to 70 and 160 meters, this time breathing a binary blend of H_2 and O_2 (4 percent O_2 and 96 percent H_2). The first dive, a short one, went perfectly; as we know, the second, after 20 minutes spent at 160 meters depth, gave rise to a fatal decompression accident, due to a material cause having nothing to do with the nature of the gas.

1.6. After his death, research on the hydrogen-oxygen blend was continued for a while in Sweden by Bjurstedt et al., who were looking for a way to cut down decompression time (15).

After that, the study of breathing mixtures based on hydrogen was abandoned for 17 years, and oxygen-helium blends became the standard support medium.

1.7. In 1966, Ralph Brauer started experimenting with the biological effects of oxygen-hydrogen breathing mixtures. A series of publications (16, 17. 18. 19. 20. 21. 22. 23) reports his experiments with mice and monkeys (macacus rhesus and squirrel monkey), in an effort to prove the existence of a protective effect exerted by hydrogen against the trembling and convulsions these animals experienced at very great depths with helium. Unfortunately some essential details are lacking, such as the procedures followed, the number of animals exposed, etc. Be that as it may, Brauer concludes from his experiments that mixtures containing hydrogen are not toxic, that their narcotic effect is slight (the narcotic power of hydrogen is supposed to be only 25 per cent that of nitrogen), and that hydrogen is an antidote to the effects of pressure or helium on the central nervous system. As to what we are concerned with, Brauer claims that he was able to maintain mice "without serious trouble" under 67 ATA, and that he kept several monkeys under 60 ATA for 24 hours, breathing a ternary oxygen-hydrogen-nitrogen mix, but he does not give the concentrations.

This series of experiments led him in October 1968 to attempt the Hydra experiment, of which we spoke earlier.

1.8. In 1967 P.O. Edel (54), after a series of theoretical studies, began human and animal experiments to reveal the feasibility of breathing oxygen-hydrogen mixtures, and to study the features of the parameters of decompression with these mixes.

From 1967 to 1971, six volunteers went through 12 simulated dives at a pressure equivalent to around 60 meters, breathing a mixture of hydrogen and oxygen containing first 4 and then 3 percent oxygen; the duration of inhalation of this mixture ranged from 10 to 108 minutes. These experiments revealed no toxic effects from the mix: no incident was recorded during these simulated dives. Some mild decompression accidents were treated with the standard methods and cured. Some biological examinations (unspecified) on the blood and urine gave normal results.

At lower depths, and for longer exposure times, Edel performed experiments with two dogs.

Number 1 was exposed for 24 hours under a pressure of 10 ATA to respiration of a hydrogen-oxygen mix with 2.5 [percent] oxygen.

Number 2 spent 39 hours under a pressure of around 31 ATA, breathing a hydrogen-oxygen mix.

The first dog showed no distress, while the second suffered a decompression accident which was completely cured by standard treatment. Edel does not seem to have been particularly interested either in any possible metabolic changes induced by hydrogen-based mixtures, nor yet in their toxic aspect, since his main concern was with decompression problems.

It is a pity that there was no physiological or anatomo-pathological investigation of the animals was performed, and that the biological investigations made during the human experiments were not more detailed. However, we have talked with Mr Edel, and the experiments he is currently working on will certainly give us new and copious information.

We can, however, accept his finding that there was no indication of narcosis or of SNHP trouble, which can reasonably be interpreted as an absence of any such symptoms, and that no long-term simulated dive by humans or dogs, or at greater depths by dogs, caused death or the onset of pathological phenomena.

1.9. In 1969, a few months after the start of our experiments, X. Fructus, R. Haquet, and J.C. Rostain at CONEX began a series of animal experiments to discover any toxicity, the level of onset and the intensity of SNHP and narcosis with hydrogen-oxygen mixes.

Their experiments and their findings can be summarized as follows:

In the initial series, six Papio-Papio monkeys were subjected for various periods to inhalation of binary hydrogen-oxygen mixes under a PIO_2 of 0.21 bars, at simulated depths of 300 to 675 meters. Decompression rates were 100 m/hr and 200 m/hr.

Monkeys numbers 1 and 2 spent 24 hours at 300 meters. Both showed a slowing and diminution in the scope of EEG activity, which became monorhythmic, and the second showed slow waves and peaks of great width. Both died, one 12 hours, the other 6 hours after removal from the caisson, and while it was possible to determine that one of the deaths was due to a decompression accident, the other is still unexplained.

Monkey number 3 spent 2 hours at 300 meters, and number 4 spent 2 hours at 500 meters and 10 minutes at 675 meters. Both survived. Number 5 showed the same EEG signs as the others, with frontal theta and slow waves, all symptoms which are reversible during decompression. Number 4 showed tremor starting at 500 meters in each dive, with EEG symptoms comparable to the earlier findings, except at 675 meters, where he showed peak-waves and a brief epileptic crisis. Everything straightened out during decompression.

Monkey number 5 died of explosive decompression as a result of a technical malfunction, after reaching a depth of 655 meters. Prior to this accident, his EEG signs were quite comparable with those shown by the other animals.

A comparative study of the effects of helium-oxygen mixes was made, and it showed that breathing H_2O_2 mixes produced characteristic modifications in the EEG (which confirms our own findings), and that shivering and epileptic crises seemed to be independent of the nature of the vector gas.

In a second series, 4 rats of the Wistar strain were given a mix of 80 percent hydrogen and 20 percent oxygen to breathe at atmospheric pressure for 40 hours. All four animals survived, and no apparent clinical or histological disturbance was observed.

In the final series, two Papio-Papio monkeys spend 24 hours in hydrogen-oxygen (PIO_2 0.21 bars) at simulated depths of 150 and 300 meters. The temperature was 55°C, and the compression rate was 60 meters per hour, slower than in the first series.

Modifications in the EEG were not so marked as in the first series. Both animals died, one 8 days, the other 24 hours after removal from the caisson, both of them showing the disturbing anomaly of a cervical abcess. "This element cannot be positively ascribed," the authors told us, "to the fact that these animals had breathed an H_2-O_2 mix, nor to the existence of an intracerebral temperature electrode." (66)

2. Brief Discussion of Hydrogen and the Dangers of Handling Its Binary Mixtures with Oxygen.

Hydrogen is number 1 in Mendelieff's classification. The atom of natural hydrogen or protium, whose atomic mass is 1.008, consists of one proton around which one electron revolves.

Protium has two isotopes: deuterium and tritium. All three isotopes are found in ordinary hydrogen, in the proportion of 99.98 percent ^{1}H, or protium, 0.02 percent ^{2}H or deuterium, and $1.5^{10}{}^{-14}$ percent ^{3}H, or tritium.

The hydrogen molecule, H_2, may have either of two forms: orthohydrogen, which has a parallel nuclear spin, in a state of rotation with an odd J number, or parahydrogen, with an anti-parallel nuclear spin, in a state of rotation with an even J number.

The magnetic moment of orthohydrogen is double that of a proton.

At ordinary temperatures, gaseous hydrogen consists of one "para" molecule for every three "ortho" molecules. The proportion of parahydrogen increases when the ambient temperature drops.

Industrial hydrogen always contains some traces of nitrogen, oxygen, and carbon dioxide; in this test, we used a mix of "N45" grade oxygen and "U" grade hydrogen produced by Aire Liquide, whose components are very pure and are manufactured for use in biology.

2.1. Physical Properties

Hydrogen, a colorless, odorless, tasteless gas, is the lightest of all the elements.

Its density in relation to air is 0.07. At 0°C and under 1 bar of pressure, hydrogen's density is 0.08986.

Hydrogen's viscosity is low: at 15°C and under 1 bar of pressure, it is 0.0087 centipoises.

Its thermal conductivity coefficient at 0°C (in cal/sec^{-1} and per cm^2) is 0.00038: it is a good conductor of heat, and of electricity, too, for that matter.

The temperature of hydrogen is very low: -239.92°C. The gas reaches atmospheric pressure at about -253°C; it solidifies at around -259°C

As a consequence, at high pressures the volume of this gas is greater than Boyle's law would predict:

If at 1 bar P.V. = 1
at 100 bars P.V. = 1.069
at 200 bars P.V. = 1.138
at 1,000 bars P.V. = 1.720

Effusion-Diffusion. According to Graham's law, the rate of diffusion of a gas through small orifices is inversely proportional to the square root of its density; since the density of hydrogen is very low, it is the fastest of all gases to diffuse: however, in practice, hydrogen-based mixtures have an annoying tendency to leak out of the bottles in which they are stored.

The diffusion coefficient of a gas is equal to the quantity of the gas which can pass through 1 square centimeter of a porous solid or through 1 cm of another pure gas, within 1 second.

Hydrogen has a high diffusion coefficient. Compared with CO_2, it is:

In	O_2	A	CO_2	H_2
H_2	0.67	0.64	0.65[3]	----
CO_2	0.041	0.142	----	0.533

In its atomic state, hydrogen diffuses through metals at ordinary temperature; it does not diffuse in its molecular state into metals unless they are heated (to red heat).

Adsorption: hydrogen is readily adsorbed by porous substances (such as charcoal, for example), and even by non-porous substances. It then penetrates the substance, where it may dissolve, forming solid solutions or specific compounds, either by adsorption proper or by chemosorption.

We observed in the course of our experiments a very swift aging of the safety seals of the caisson: the seals, which are made of cast iron, showed a change in appearance after several hours' operation under hydrogen. Several experiments were cut short as a result of early rupture of the safety seal, which brought about explosive decompression of the animal.

2.2. Chemical properties

Hydrogen as a rule is not very active when it is cold, except for its active forms. When heated, or in the presence of suitable catalysts, it forms a number of chemical reactions.

Hydrogen is univalent, strongly electro-positive, and thus close to the metals.

Chemical combinations

Hydrogen combines directly with most of the metalloids, as well as with the alkaline and alkaline-earth metals. The four halogens

form hydroacids with hydrogen, the reaction speed and the heat given off declining from fluorine to iodine.

In the presence of oxygen and at the temperature of red-hot iron, or at ordinary temperatures in the presence of a catalyst (platinum foam), water is formed. The reaction is highly [illegible].

Hydrogen also combines with sulphur at around 250°C, and with nitrogen to yield ammonia at high pressure and in the presence of catalysts.

Hydrogen forms a number of compounds with carbon, such as CH_4 (at around 1,100°C) or $(CH_2)^2$ in an electric arc.

With the alkaline and alkaline-earth metals and at around 350°C, hydrogen yields crystalline hydrides soluble in water, such as NaH or CaH_2.

But it is hydrogen's reducing properties which are best known: this element is very greedy for oxygen and chlorine, and it can reduce many of their compounds. It reduces the oxides of sulphur, nitrogen, arsenic, the precious metals, lead, copper, and iron (a reversible reduction).

In the presence of a catalyst there will be a reduction, then a hydrogenation: in the presence of platinum, the nitrogen oxides with hydrogen will yield ammonia; in the presence of reduced nickel, carbon dioxide will yield CH_4, etc.

This is how coal oils are catalytically hydrogenated to produce gasoline, and this is how organic oils are hardened.

And so hydrogen is a very active element, both chemically and physically. It is of course more active when it is found in the form of nascent hydrogen, and even more so in the form of atomic hydrogen.

Let us not forget, either, that when ionized, hydrogen defines the pH or acidity of solutions.

2.3. Dangers of Explosion of Hydrogen-Oxygen-Based Mixtures

In certain proportions, hydrogen and oxygen mixtures are explosive.

Le Chatelier's law sets the flammability threshold at:

4.65 and 93.9 percent hydrogen in oxygen.

The higher figure was obtained from studies by the European Propulsion Company (92): the binary mixture of hydrogen and oxygen at 94/6 percent does not explode.

American work done by the Bureau of Mines and by Dorr at Ocean Systems, Inc., found slightly lower thresholds for oxygen in hydrogen: 3 to 4 percent.

If we accept this figure, which A.Zetterstrom also used, we can say that hydrogen-oxygen mixtures containing at most 4 percent oxygen involve no danger of explosion. So these are the ones to be used for diving, meaning that at normoxy (PIO_2 = 0.21 bar) these binary mixtures can be used from 5 ATA (40 meters) depth and below.

3. G.E.R.S. EXPERIMENTS

3.1. Experimental Equipment

The experimental apparatus, although it was designed in principle at the start of experimentation, was nevertheless subjected to some improvements after the initial tests.

The animals were placed in a cylindrical caisson whose internal volume was 40 liters. The maximum operating pressure for this caisson was 31 bars, which is why all our experiments were conducted at 29 bars. This was a very good thing, because we quickly noticed that the safety seal deteriorated very quickly in the presence of hydrogen, and if we had chosen an experimental pressure closer to the limit, we should probably have discovered even more premature seal breaks.

Preparation of the Animals

With only a few exceptions, all our animals were prepared in the following way:

Six electrocorticographic electrodes and one undifferentiated electrode were placed on the animals' crania 10 days before the experiment. On the morning of the experiment, these electrodes were connected with a braid of wires 30 cm in length to a junction box placed over an airtight conduit pass. At the same time, two wires were inserted into the skin by means of a Reverdin needle for the ECG recording. All these wires were fastened to the animals' backs with adhesive tape, taking care that the ECG wires were separated from those for the EEG.

Some of the rabbits and all of the rats were used without instrumentation.

The problem of restraining the animals is worth a closer look. During the first tests, the animal was completely free in its movements, and on several occasions it gnawed the wires. We then tried using a stockinette shirt for restraint, putting the rabbit's head and paws through "ad hoc" holes, and lacing it up the

back. The shirt was fastened to the floor of the caisson by means of hooks attached to rings. The animal could move, but its movements were restricted. As we went on some drawbacks appeared; for one thing, this restraint caused decompression accidents when we returned the animal to the surface. In the end, the system we found most satisfactory was a kind of little cage in which the animal was free to move about within certain limits, and which protected the fragile devices, such as electric wires, etc.

Arrangements inside the Caisson

In addition to the restraining cage, the caisson contained a thermo-couple, duly set in situ for each series of experiments, a vibrator to rouse the animal, a set of light reflectors and diffusers to get good lighting from an iode bulb located outside a porthole, a feeding dish in which a known number of synthetic food pellets were placed, a water dish, and a basket of soda-lime.

Outside the caisson, a double coil of electrical resistance took care of heating. Half was wound in one direction, the other half in the other, so as to avoid setting up an electrical field and its possible biological effects. A layer of neoprene foam provided mechanical protection for the heating coil, as well as a degree of thermal insulation.

A mobile TV camera was positioned outside a porthole to enable us to watch the animal. Since visibility was often only mediocre, we had to send in a diver from time to time to make direct observations.

In order to cut down the possible effects of an explosion, the entire caisson and its apparatus was immersed under 6 meters of water in the Port of Toulon, and attached by means of a cable with 18 insulated wires to the recording apparatus (REEGA TR VIII" Alvar) and the oscilloscope (Reegascope-Alvar) on the quay. A pontoon held the gas tanks and the control panel for pressure, admission of the gases, analysis of the caisson atmosphere, and copper tubes fastening the caisson to this assembly.

Dive Parameters

Analyses taken every 15 minutes on gases tapped from the caisson (gaseous-phase chromatography on a Beckman GC-2A) enabled us to be sure that the composition of the atmosphere in the caisson was right, and that there was no noticable pollution, CO_2 or other.

The PIO_2 was different according to the experiments: initially we tried moderate hyperoxia at 0.40 to 0.49 bars, in order to obtain good alveolocapillary diffusion of the oxygen; later on, the results of our comparative experiments at hyperoxia led us to select a PIO_2 closer to normoxy: 0.29 bars.

Similarly for the temperature: we set it at 29°C for our initial experiments, but on the advice of Schreiner of Ocean Systems we later moved it up to 32 and then 34°C, since that figure was closer to thermal neutrality in an oxygen-hydrogen mix.

Pressurization was obtained up to 10 bars with the help of a 16-percent oxygen mix with helium; a 30-minute platform enabled us to sweep at that pressure with an O_2-He mix at 2 percent oxygen, until we got a P_{IO2} of 0.21 bars. We then resumed compression, backing up with a sweep with an O_2-H_2 mix containing 1.0 to 1.7 percent oxygen, until we had 29 ATA. Compression lasted 60 to 90 minutes in all, and when we hit bottom the atmosphere was a binary O_2H_2 mix.

From then on, occasional ventilation assured a proper P_{IO_2} in the caisson.

The stay on the bottom differed according to the series:

In the Lapinabloc series, the animals were kept saturated until their death (see below) and the cadaver was subsequently decompressed. Some animals remained at saturation for a number of hours stipulated in advance: one unwired rabbit stayed 14 hours, and four unwired rats stayed for 72 hours.

In the Lapinacourt series, the animals remained on the bottom 30, 45, 60, or 120 minutes according to the case: some were kept under hydrogen-oxygen for the entire stay and were then decompressed, others breathed the hydrogen-oxygen mix for half their stay, and were given helium-oxygen for the second half, prior to decompression.

Three continuous decompression tables were used, according to the length of stay at the bottom. According to the table, the 10-minute, 30-minute, and 80-minute tables were assigned saturation coefficients 1.70-1.60 1.50 or 1.60 - 1.50 - 1.40 or 1.50 - 1.40 - 1.30: the decompression times were respectively 10 hours 1 minute, 11 hours 6 minutes, and 13 hours 9 minutes.

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We ran a lot of other experiments which are not reported here, experiments which helped us to establish our procedure, or experiments which were aborted as a result of accidents. The experiments reported here are homogeneous insofar as procedures are concerned.

3.2. Lapinabloc Experiments and Experiments with Saturated Rats

Five rabbits weighing 2.5 to 4 kilograms, fitted with EEG and EKG electrodes implanted in the hutch were placed under saturation under the aforementioned conditions. The temperature was 29°C, the PIO_2 from 0.40 to 0.50 bars.

The results can be summed up as follows; in all the animals we found:

a gradual decline in the amplitude of the EEG potentials, leading to cortical electrical silence in 7 to 20 hours. The flattening of the graph was interrupted by brief renewed spurts of activity at increasingly longer intervals. Isolated large slow waves at irregular intervals of several seconds preceded electrical silence by several minutes.

During the first hours of the dive, cardiac frequency declined. For several hours, (4 to 25 hours after the onset of EEG silence), the cardiac rate was very slow. Extrasystoles and ventricular fibrillation preceded EKG silence.

During all this time motor and respiratory activity (stimulated by the vibrator in the caisson) were reduced, and progressively attenuated.

The animal cadaver was decompressed after cardiac arrest.

Experiments identical with these from the experimental point of view, run at the same time on three rabbits, but under an oxygen-helium mix, and earlier experiments under similar conditions in an O_2-He atmosphere showed no lethal or grave pathological phenomena. All these animals survived.

One final rabbit weighing 3 kilos and without wiring was subjected for 14 hours to inhalation of O_2-H_2 under 29 ATA, with the P_{IO_2} this time 0.29 bars and the temperature 34°C, then sacrificed by fast decompression for histological examination. Its behavior was identical with that of its predecessors.

So as to see whether the overall phenomena observed in rabbits could be repeated in other species, four male rats of the Wistar strain were placed two by two in the caisson and compressed under oxygen-hydrogen for 72 hours. The general procedure was identical with that used on rabbits, the temperature was 34°C and the PIO_2 from 0.25 to 0.29 bars.

One rat died after 56 hours under 20 ATA, three died either at the end of their stay at 29 ATA, or at the beginning of decompression.

Tissue samples were taken for histological and histoenzymological examination (after freezing at -20°C).

3.3. Lapincourt Experiments (short dives) (44)

These were dives lasting 30, 45, 60, or 120 minutes in an oxygen-hydrogen atmosphere under a pressure of 29 ATA; the temperature was set at 32 or 34°C. The rabbits weighed 3 to 4 kilos.

In an initial series, four rabbits were placed under pressure of as much as 29 bars according to procedures identical with the foregoing, but compression lasted only 40 minutes, thanks to more effective ventilation. The stay on the bottom lasted a total of 1 hour, 30 minutes under oxygen-hydrogen ensuring a PIO_2 of 0.46 bars, followed 30 minutes under continuous sweeping with oxygen-helium at 2 percent oxygen. All these rabbits were brought back to the surface alive. The electrical recordings were normal from beginning to end, showing only a slight decline in the amplitude of the EEG between the second and third hours (during decompression).

In a second series two rabbits were subjected, under the same conditions, for 30 minutes and 40 minutes, to inhalation of an oxygen-hydrogen mix ensuring a PIO_2 of 0.29 bars. The first died at the start of decompression, the second was sacrificed by fast decompression starting at the moment when the pressure reached 3 ATA.

The third series consisted of six rabits which were placed as before under pressure in oxygen-hydrogen at a PIO_2 of 0.46 bars. The length of stay was 60 minutes for five of them, but only 50 minutes for the sixth. A break in the security seal caused its explosive decompression. The other five were decompressed in about 10 hours. Three died during decompression, one when it was removed from the caisson, one died a few hours after removal, and one survived. The EEG amd EKG tracings were similar to those of the other rabbits in the Lapinacourt experiments. Death was apparently attributable to a decompression accident, although we were unable to find any clear signs to support this hypothesis. Emphasis must be placed on the fact that the rabbits readily tolerated the same conditions of dive and decompression when they were breathing oxygen-helium.

Two rabbits, under the same overall conditions, were made to breath the oxygen-hydrogen mix for 1 hour, then a 2-percent-oxygen oxygen-helium mix for another hour. We were able to bring them back to the surface without any difficulty.

As we said earlier, the comparative experiments under helium gave rise to no anomalies, and the animals tolerated both dive and decompression perfectly.

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If we recapitulate the results, we find in our experiments:

That all the animals, rabbits or rats, subjected to very long stays in atmospheres of normoxic or slightly hyperoxic mixes of oxygen and hydrogen, under a pressure of 29 ATA, died while exhibiting a body of similar symptoms. It should be noted that there are inter-species differences, such as the fact that white rats seem to be more resistant than rabbits.

Short exposures are better tolerated, the more so as the exposure to hydrogen is shorter. This finding is even better when care is taken to have the animal breathe an oxygen-helium mix prior to decompression.

It was impossible to pinpoint the cause of the animals' death; it looks as if they had trouble bearing up under the onslaught of decompression, even very slow decompression, once they had been exposed to hydrogen. Apparently we were lucky in finding the outermost limit of exposure for rabbits, which is on the order of 30 to 60 minutes, according to the individual.

3.4. Anatomo-pathological and Histoenzymological Findings

Autopsies were performed immediately after sacrifice or as soon as possible after the accidental death of the animals. Fixation of the organs removed for histology: central nervous system, heart, skeletal muscle, liver, kidneys, gonads, lungs, hematopoietic marrow, and bone was done with formol-alcohol-acetic. After inclusion in paraffin, the routine dyes (Hemateine, Eosine, Safran), or for the nervous system the Mallory colorants and methylene blue according to Nissl were used. For histoenzymology, the organs were frozen and kept at -20°C.

a. Studies on Various Conditions of Anoxia and Hyperoxia
Rabbits perfused with CNK (dose 1 $mg/kg^{-1}/1\ hr^{-2}$).
(Corriol et al., 50,51.)

Involvement of the cerebral level shows nuclear pycnosis and soft cytoplasmic disintegration lesions of areas H4 and H5 of the hippocampus, with the cortex and Purkinje cells intact: this is a paradoxical finding since the cortex is more sensitive to anoxia than is the hippocampus major.

Rabbits, rats subjected to breathing pure helium or nitrogen under normal pressure (Paramedian saggital sections of the encephalus)

Notice the particular involvement of the terminal sector of the hippocampus major (areas H4 and H5 of Rose),of the cortex, and of Purkinje's cells. These are the areas classically attacked by anoxia.

Rats in moderate hyperoxia (0.40 to 0.60 bars) under pressurized air.

This experiment enabled us to see that in addition to the banal congestive lesions in the various viscera there are major lesions on the brain level to the Purkinje cells (50 percent affected), of areas H4 and H5 in the hippocampus major and Lancisi's striae, as well as in the cortex, predominantly in Brodman layers 3 to 5.

Rats under pressure in pure oxygen for 1 hour, at 4, 6, and 8 bars.

The cellular involvement in the brain touches the cortex, Ammon's horn, and Purkinje's cells.
These lesions, though located in the same places as the anoxia lesions, are nevertheless different from them: condensation of the cytoplasm and of the chromatic substance, as well as nuclear pycnosis, are incomplete, and the appearance of the cells is more blurred.

b. Studies of Animals Exposed to Hydrogen-Oxygen

Rabbits subjected for 1 hour to moderately hyperoxic hydrogen-oxygen

You find pictures of vascular congestion, particularly marked on the level of the lungs, where their appearance is very like that of hypertrophic reticulated pneumonia; generalized blistering phenomena which may be more or less important but which apparently entail no vascular or cellular damage; and on the level of the encephalum some signs of cellular damage suggesting hypoxia; nuclear pycnosis, cytoplasmic homogenization predominant on layers 3 and 4 of the cortex, occasionally involving the cells of areas H4 and H5 of Ammon's horn.

Saturated rats under normoxic O_2H_2

Comparable lesions on the level of the encephalus: only the hippocampus is involved.

Rabbits subjected to normoxic hydrogen-oxygen for 14 hours, 1 hour, 45 minutes, and 30 minutes.

The same lesions are found, particularly on the level of the encephalus. As the length of exposure increases, the neuronal involvement is completed. In the rabbit who spent 14 hours in the hydrogen-oxygen mix, it affects, in addition to the cortex, areas 4 and 5 of Ammon's horn and the Purkinje cells.

Saturated rats in normoxic oxygen-hydrogen (Histoenzymology)

The quite inconclusive findings are summed up in the table on page 17.

4. DISCUSSION

It is quite difficult to make comparisons between our experiments and those of the other authors we cited earlier: the experimental animals are not the same (guinea pigs, mice, rats, rabbits, cats, dogs, monkeys of various species, men), the pressures range from 1 to 150 ATA and higher, the mixes are different (binary and ternary), the PIO_2s are different, the procedures, when they are described, are different, etc....

4.1. Even so, we find on the physiological level that:

of all the animals we exposed under pressure to the oxygen-hydrogen mix, only those who were exposed for short periods survived.

a similar observation can be made concerning the results of experiments by Fructus, Naquet, and Ristain on monkeys.

humans exposed for short period of time to this mix displayed no pathological signs (Zetterstrom, Edel).

The findings of P.O. Edel on dogs and of Brauer on rats and monkeys, however, flatly contradict those results.

We can set aside the experiments made at atmospheric pressure by Lavoisier and Fructus-Naquet, because they are quite different; the death of Lavoisier's guinea pigs was consecutive beyond doubt to exhaustion of the available oxygen and to hypercapnea, and we argue that little animals like rats have tolerated prolonged exposure to oxygen without harm.

4.2. There is also some indication of sensitivity to hydrogen, which appears to depend on the animal species.

4.3. The length of exposure seems to be an important factor in the case of a species sensitive to oxygen-hydrogen. There is doubtless a time threshold below which hydrogen is tolerated without harm.

4.4. Similarly, the pressure under which oxygen is inhaled seems to play some role.

ENZYMATIC ACTIVITY IN SOME ORGANS OF RATS

in H_2-O_2 at 29 Bars for 72 Hrs

		Succino-Déhydrogènase	Cytochrone Oxydase	Mono-Amine Oxydase	A T Paso	Glucose-6-P Déshydrogènase
Brain	*T	+ +	+ + +	+ +	+ + +	0
	N°1	+ +	+ +	+	+ + + +	0
	N° 2	+ +	+ +	+	+ + +	0
Kidney	T	+ + +	+ + +	0	/	0
	N° 1	+ + + +	+ + + +	0	+ + + +	0
	N° 2	+ + + +	+ + + +	0	+ + +	0
Liver	T	+ +	+ + +	+ +	+ + + +	-
	N° 1	+ + + +	+ + + +	+	+ + + +	0
	N° 2	+ + + +	+ + + +	+	+ + + +	-
Lung	T	+ + + +	+ + + +	0	+ + + +	0
	N° 1	+ + + +	+ + + +	0	+ + + +	0
	N° 2	+ + + +	+ + + +	0	+ + + +	0

* T = Control specimen

		6-P-Gluconate Déshydrogèna -se	L. Malate Déshydrogè -nase	Glutamyl Déshydrogè -nase	Isocitrate Déshydrogènase	Lactate Déshydrogènase
Brain	T	+ +	+ + + +	+	0	/
	N° 1	+ + +	+ + + +	+ + +	+	/
	N° 2	+ + +	+ +	+	0	/
Kidney	T	0	+	+	+	/
	N° 1	+ +	+ + +	+ + +	+	/
	N° 2	+ +	+ + + +	+ +	+	/
Liver	T	/	+ + + +	+ + + +	+	/
	N° 1	+ + +	+ + + +	+ + + +	+ +	/
	N°2	+ + + +	+ + + +	+ +	0	/
Lung	T	0	+ + +	+	+ +	/
	N°1	+ +	+ + +	+ + + +	0	/
	N°2	+ +	+ + +	+ +	0	/

4.5. Fructus, Naquet, and Ristain found EEG modifications under O_2-H_2 which resembled those we found, and seem to be specific. These same writers point out that the use of hydrogen-based mixes does not seem to protect against SNHP disturbances, contrary to Brauer's assertions.

4.6. What might the lethal factors of the oxygen-hydrogen mix be?

The pressure factor per sec unquestionably plays a part in the constitution of SNHP (8), and as such may play a contributing role in the symptoms we observed.

The partial pressure of oxygen is a second factor to consider: while some experiments (Edel, Cornex, some GERS experiments) have adhered to normoxy, most of our experiments, in order to maintain normal alveolocapillary diffusion (Cf the observations of Chouteau, Guillerm, and Hee (47,70) were run at moderate hyperoxy.

Balouet and Barthelemy (9) used Wistar-strain rats to study the anatomo-pathological effects of breathing air for 24 hours under pressure guaranteeing a PIO_2 analogous to that of the GERS experiments. They found nuclear alterations in the CNS, although less pronounced than with oxygen-hydrogen respiration, and pulmonary congestion with a moderate Lorrain-Smith effect. These lesions were regressive after a return to a PIO_2 of 0.21 bars.

This indicates that moderate hyperoxy will cause lesions, but most of all that some of the anatomo-pathological findings on animals breathing hydrogen-oxygen have to do with that hyperoxy.

The possibility of impurities in the respiratory mix, while not very likely, cannot be absolutely ruled out.

The same goes for the effects of the environment--isolation, confinement, etc., which are already there in helium dives, could have played a contributory role.

The prime factor, though, seems to be hydrogen. This supposedly inert gas, under hyperbar conditions and under partial pressure -- which of the two remains to be determined -- seems to display a degree of toxicity.

This might stem from disturbances occurring at the level of the respiratory chains and of the oxyreduction processes for high partial pressures of hydrogen (Chouteau et all., 43, 47; Michaud et al., 84). Hydrogen does indeed play a part in the definition of the normal oxygen reduction process. Cf for example Nernst's equation:

$$E = \frac{RT}{ZF} \text{ Log } \frac{(H+1)}{(H2)^{\frac{1}{2}}} - \frac{RT}{ZF} \text{ Log } \frac{(H+)C}{(H+)C}$$

Even a cursory examination of Nernst's theory is suggestive: one simple idea that comes to mind is the definition of the RH_2 potential of an electrode; it involves the concept of a molecular hydrogen pressure, and it is reasonable to assume that the transgression of such an elementary law of thermodynamics as this might quite possibly entail consequences.

Naquet and Rostain do not reject this hypothesis out out of hand: they admit that the mechanisms reflecting neurological disturbances encountered are of several orders: toxic, metabolic, or even something else. (98)

Corriol et al. (50.51) got a similar symptomology to ours with the O_2-H_2 mix when they perfused a rabbit slowly with a solution of potassium cyanide at a dosage of 1 mg/1kilo^{-1}/1 hr^{-2}. The cyanide inhibited cytochrome oxydase (Paulet, 87), and this would tend to strengthen the hypothesis of some action on the level of the respiratory chains,

The cerebral histological lesions encountered are of the anoxic type:

on the cellular level, it is always the same neuronal lesion which is encountered: cytoplasmic condensation lesions with hyperchromasy, nuclear pycnosis, and cellular retraction.

topographically, we find in rabbits subjected to hydrogen-oxygen at normal oxygen level a localization in the Purkinje cells, at a number of neurons in Bordman zones 3 and 4 of the cortex, and in less intensive involvements of some neurons in sectors H4 and H5 and in the horn of Ammon. After short dives the lesions are far less marked, increasing in importance as the length of the dive from 30 to 60 minutes, which confirms the impression that this length of exposure is an important factor. Rats, which are clinically tougher than rabbits, show under saturation come histological differences from rabbits, with the predominant damage in the hippocampus major.

It is therefore legitimate to argue that the toxicity of oxygen-hydrogen mixes has something to do with an anoxic phenomenon, whose precise mechanism remains to be singled out.

In Wistar-strain rats, for the organs examined and for the enzymatic activities investigated, there is no significant difference between the control rat and the rat made to breathe O_2-H_2. This calls for comparison with what Schreiner personally told us in 1968, when he said that he had found no anatomical, pathological,

or enzymological anomalies in rats breathing hydrogen-oxygen. You will note, however, that these lesions are also found at normal oxygen levels under oxygen-hydrogen.

CONCLUSION

Oxygen-hydrogen mixes, which, because of their lower density, apparently ought to improve the dynamics of ventilation and of alveolocapillary gaseous exchange, offer great hopes for pushing back still further the depth limit reached with oxygen-helium mixtures.

However, we have discovered a toxic effect of these mixes, which seems to occur only after a certain length of exposure, which differs according to the animal species considered, and this leaves us the hope that oxygen-hydrogen mixes can be used under certain conditions for short periods of time in human dives. This use by man must not be contemplated until definitive conclusions have been reached in animal experiments.

Experimentation should be continued, so as to find out precisely:

the role of partial hydrogen pressure.

There should be systematic experiments done under normoxy PIO_2, running from atmospheric pressure to extreme pressures, and under these conditions there must be a definition of the PIO_2s which are adequate to ensure good hematosis without causing pulmonary or nervous lesions;

the ternary pxygen-nitrogen-hydrogen mixes must be systematically tested. The optimum proportions of their components remain to be defined;

variations from species to species, which have thus far only been vaguely indicated, must be systematically established;

studies on the EEG and EKG must be completed with EMGs, a study of the potentials hinted at, and measurement of the Pa_{O2} on the cerebral level...

finally, neurophysiological, anatomopathological, and histoenzymological research must be completed, so as to study any enzymatic disturbances on the level of the metabolic routes and the respiratory chains. Humoral modifications are still to be explored.

CAPTIONS

1. Hydrogen experiments: Gas circuit

2. The experimental rabbit, electrodes plugged in, and the arrangements inside the caisson.

3. The caisson rests on the pier before being lowered into the water.

4,5. Lowering the caisson into the water.

6. The diver jumps into the water to help guide the caisson to rest on its base on the bottom.

7. The bottle rack on the pontoon, behind the derrick.

8. The cabin housing the valve and manometer controls, from which the animals' dives are controlled.

9. EEG and EKG: A. Before compression. B.C.D.E: Respectively 2,4,6, and 8 hours at 29 bars in O_2-H_2 (PIO_2 = 435 mb). Note the very marked diminution in the EEG amplitude, the disappearance of all organized activity after the 6th hour and the very massive terminal bradycardia (EEG derivation: 1,2, right longitudinal; 3,4, left longitudinal; 5,6,7, interhemispherical from front to back).

10. Evolution of EEG amplitude (percentage of initial amplitude) and of cardiac rate per minute in a rabbit breathing an O_2-H_2 mix under 29 bars (PIO_2 = 435 mb). On the ordinates, EKG frequency; on the abscissas, time in hours.

11. Cortex of a rabbit which breathed the H_2-O_2 mix at 29 bars for 1 hour. Nissi Blue dye. X 25. Anoxia: selective neuronal lesions in Bradma layers 3 and 4.

12. Anatomo-pathological observations of rabbits breathing an H_2O_2 mix at 29 bars for 1 hour. PIO_2 [illegible]

13. Ammon's horn of a rat breathing the H_2-O_2 mix at 29 bars for 72 hours. Nissi dye. X 100 Anoxia: neuronal homogenization lesions in the sectors.

14. Anatomopathological findings of cerebral lesions in rats breathing the H_2O_2 mix for 72 hours at 29 bars, PIO_2 [illegible].

15. Diagram of the hippocampus and Horn of Ammon.
Areas in pink: [balance illegible]

16. Horn of Ammon in a rabbit perfused with a KCN solution. Nissi Blue dye. X 400

17. Cerebral lesions after potassium cyanide perfusion in rabbits.

18. Horn of Ammon in a rabbit breathing pure helium at normal pressure. Nissi Blue stain. X 250.

19. Lesions caused by cerebral anoxia and their location after inhalation of pure helium and nitrogen at normal pressure.

20. Anatomo-pathological findings [balance illegible]

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CSO: 8019/0117

INERT GAS NARCOSIS AND ANIMALS UNDER HIGH PRESSURE

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INTRODUCTION

SYMPOSIA OF THE
SOCIETY FOR EXPERIMENTAL BIOLOGY

NUMBER XXVI

THE EFFECTS OF PRESSURE ON ORGANISMS

Published for the Society for Experimental Biology
CAMBRIDGE: AT THE UNIVERSITY PRESS
1972

III-10-168

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INTRODUCTION

Classically the depth to which men could dive was limited by nitrogen narcosis to about 70 m of sea water (about 7 atm). This problem was overcome by the substitution of the less soluble gas helium for nitrogen as the inert gas dilutant required to prevent oxygen poisoning (Hildebrand, Sayers & Yant, 1928). However, removal of the nitrogen narcosis barrier did not lead to an immediate quest for the limits under helium diving until the impetus provided by the revolutionary 300 m ($\approx$ 30 atm) dive of Hans Keller in 1963 (Keller & Bühlmann, 1965). Since that time considerable attention has been devoted to the possibilities of deep diving, culminating in the recent chamber 'dives' to simulated depths of 450 m ($\approx$ 45 atm) by the British Navy (Bevan, 1971; Bennett, 1971) and to about 510 m ($\approx$ 51 atm) by a French group. Although the conditions had to be closely controlled and compression carried out slowly, neither of these simulated dives encountered problems sufficient to indicate the likely depth limits of human diving. The question of what factors will limit man's progress to greater depths remains. To answer such a question we must turn to work on animals.

EFFECTS OF HYDROSTATIC PRESSURE

The effects of hydrostatic pressure on many biological systems have been extensively investigated. The classic work of Regnard (1891), extended by Ebbecke (1936), Cattell (1936) and many others (for reviews see Fenn, 1969 and other papers in this volume), showed in general that in aquatic animals the first major effect of pressure is a general stimulation of the central nervous system at pressures above about 50 atm. At higher pressures (200–300 atm) spontaneous muscle contraction occurs and the animals become paralysed. Still higher pressures prove lethal (400–600 atm). At the greatest depths in the ocean the pressure would be about 1100 atm.

Studies of mammals exposed to high pressures are complicated by the problem of distinguishing between the effects of pressure *per se* and those

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of the gases breathed. Thus the first effect to be observed when mice are exposed to hyperbaric nitrogen is complete anaesthesia at 35–40 atm (Miller, Paton & Smith, 1967). Such anaesthesia may be caused by nearly all inert gases and only helium, neon and hydrogen may be employed for studies at higher pressures (Miller, Paton, Streett & Smith, 1967; Brauer & Way, 1970), although it has proved possible to expose mice to hydrostatic pressure alone, but this can only be achieved when core temperature is at about 20 °C (Kylstra, Nantz, Crowe, Wagner & Saltzman, 1967).

The most extensive mammalian studies involving pressures of the order of 100 atm have been carried out on mice and the principal effects of pressure have been noted by several groups. (Brauer, Way & Perry, 1968; MacInnis, Dickson & Lambertsen, 1967; Lever, Miller, Paton & Smith, 1971*a*, *b*). More recently, studies have been carried out on primates and goats with generally similar conclusions (Chouteau & Corriol, 1971; Rostain, Fructus & Naquet, 1970; Brauer, Way, Jordon & Parrish, 1970). One may summarize the major effects of raising the ambient pressure with helium as follows:

(1) Unco-ordinated tremors (the 'fasciculation' of Brauer *et al.* 1968). Trembling of the limbs and jerky unco-ordinated voluntary movements have been observed by most workers on mice. Onset pressure seems to depend on compression rate and may occur between 35 and 100 atm, though most generally at about 60–70 atm. These tremors appear to remit after a short period at pressure, and they have been observed in primates and men at rather lower pressures.

(2) Convulsions occur at a higher pressure than tremors and may be regarded as a culmination of the latter effect. Often the limbs are fully extended caudally and the body is arched in what may be described as a 'stretch fit'. This is followed by collapse, but if death does not intervene the animal recovers after a moribund period of a few minutes. Convulsions may be suppressed with narcotic gases and their onset pressure appears to depend on the strain of animal (Brauer & Way, 1970). In primates the onset pressure is lower, generally about 50–60 atm, though again the threshold may be dependent on compression rate. These tremors and convulsions appear to originate in the brain and are evidently caused by pressure *per se*, according to the elegant work of Kylstra *et al.* (1967) on liquid-breathing mice. They exposed mice totally immersed in a highly oxygenated fluorocarbon liquid at 20 °C to hydraulic compression. Maximum pressures were attained in 10 minutes. They observed tremors in the range 50–80 atm and tonic convulsions ('stretch fits') at 50–100 atm. In three mice with transected spinal cords compression spasms occurred cranially to the lesions, whilst the limbs caudal to the lesions remained

flaccid. At the present stage of exploration, men have not developed convulsions even at about 50 atm, however the results of EEG monitoring give grounds for concern (Bennett, 1971).

(3) Respiratory distress and mouth breathing have been noted in mice at pressures above 90 atm.

(4) Death occurs at pressures between 130 and 170 atm, apparently depending on compression rate, although most workers have not carried their studies to such high pressures. About half the deaths observed were associated with convulsions; the remainder occurred either suddenly, or, especially at higher pressures, after a period of apparent unconsciousness (Miller, Paton & Smith, 1971). In the latter cases the cause of death was not obvious. Recent observers report collapse and death in goats at 110–120 atm (Chouteau & Corriol, 1971) and cardiac arrest in squirrel monkeys (Langley, 1970). Both these observers report oxygen to be beneficial, as it is with rats and mice (Dossett & Hempleman, 1972).

(5) No narcosis has been observed in oxy-helium, except under hypothermia (Miller *et al.* 1967), and mice have been successfully decompressed from 122 atm with no apparent ill effect (MacInnis *et al.* 1967), even though they have approached close to the lethal limit. However, mice that have exhibited convulsions around 100 atm are more susceptible to convulsions on subsequent compressions, possibly indicating brain damage (Brauer, 1970).

The work of our hyperbaric pharmacology unit at Oxford has been largely aimed at identifying the effects of pressure *per se* and studying how they are modified by the pharmacological and physical properties of the inert gases breathed. Our early work was carried out in a very small chamber using relatively fast compression times. More recently we have carried out experiments in a larger chamber capable of working to 300 atm (Plate 1). Mice are exposed in pairs in large-mesh wire cages over soda-lime trays. A powerful fan, driven by an induction motor, ensures gas mixing and carbon dioxide scrubbing. The chamber temperature is monitored by thermistors and maintained at about 30 °C. Initial oxygen partial pressure is 1 atm and this is allowed to fall to not less than 0.5 atm.

The influence of compression rate has been fully emphasized in a previous paper (Dossett & Hempleman, 1972). We find that not only are the thresholds for tremors and convulsions raised somewhat by slowing the compression rate, but so also is the lethal limit – very slow compressions being particularly beneficial. Thus at a compression rate of 1.25 atm min^{-1} nine mice died at 135 ± 3 atm, whereas at a compression rate of 0.5 atm min^{-1} three mice died at 159 ± 4 atm (Lever *et al.* 1971*b*). Since most of our work has been of a comparative nature, and extremely prolonged

experiments are technically difficult, we have adopted a compression rate of 1.25 atm min^{-1} as standard.

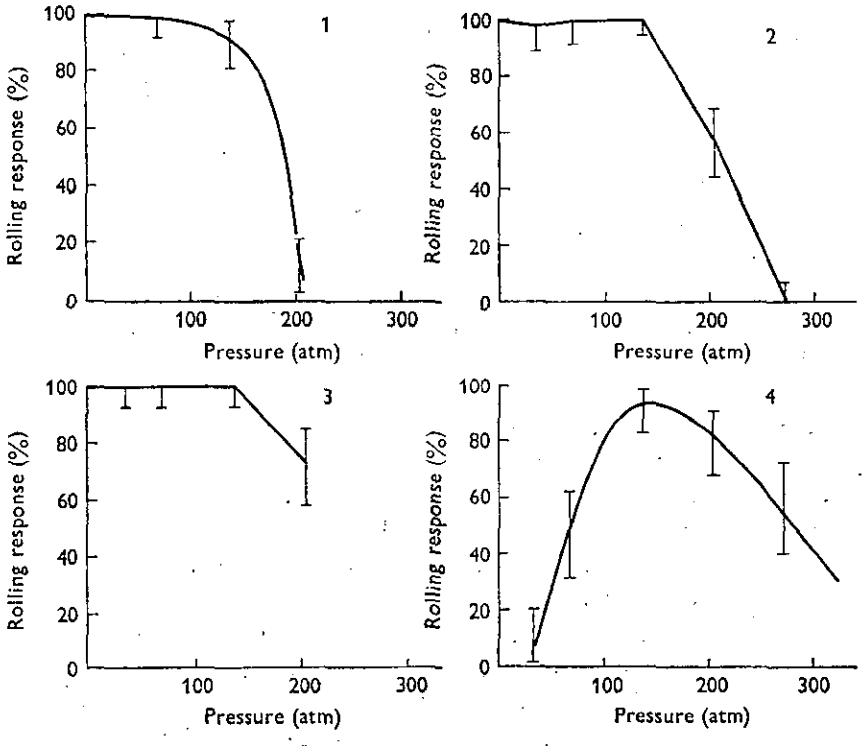
We first examined the influence of raised inert gas density, which might be expected to cause respiratory distress. By substituting neon for helium as the inert gas dilutant, the gas density may be increased five fold. We observed mouth breathing at 95 atm, but although respiratory distress appeared more marked, the lethal threshold was not lowered compared to helium. This suggested that death was not related to the load imposed on the respiratory system while breathing at high density, a result confirmed by studies of mice breathing CF_4 at 20 atm (Miller *et al.* 1967), a medium more than three times as dense as that in which mice die in He/O_2. It seemed likely to us, therefore, that death was related to pressure *per se*.

In order to investigate the effects of pressure *per se* in this range we have carried out studies on the Italian Crested Newt (*Triturus cristatus carnifex*). This animal has the advantage that it can be exposed to both hydrostatic and gas pressures. It resembles the mouse in having an extremely rapid righting reflex and is anaesthetized by inert gases at comparable pressures. We have been able to measure its ability to follow a revolving drum (rolling response) at pressure, and in this way to quantify the effects of narcosis as well as paralysis.

First of all, we established the effect of hydrostatic pressure alone (i.e. when the chamber is completely filled with water) on the rolling response. Fig. 1 shows that as the pressure is raised failure to follow the drum begins at about 100 atm and is complete by about 200 atm, when the animal is almost completely paralysed. Partial paralysis is seen at lower pressures where muscular contraction first manifests itself in the rear legs. Animals subjected to the highest pressures recover on removal of pressure. The central nervous system is apparently not grossly impaired, for partially paralysed newts always struggle to right themselves.

Exposure to helium and neon showed very similar effects, although an equivalent level of paralysis appeared at slightly higher pressures, indicating that these gases provide some protection (Figs. 2 and 3).

Having established that pressure imposes a physiological depth barrier due to failure of the muscles or their control, we next asked if drugs might ameliorate the effects of pressure. The most important observation here is that of Johnson & Flagler (1950), who found that tadpoles exposed to hydrostatic pressure responded with increased activity at 130 atm and paralysis at 300 atm. If they were first anaesthetized with 2–5 % ethanol, however, activity was restored by pressures of between 130 and 300 atm. Accordingly, we exposed mice anaesthetized with 45 atm of nitrogen or 0.1 mg g^{-1} sodium pentobarbitone (injected subcutaneously) to com-



Figs. 1 to 4

Fig. 1. Rolling response of newts as a function of hydrostatic pressure (in water). Error bars indicate the 95 % confidence limits. All ten animals were exposed at each pressure. The temperature was 20 °C and the rotation speed 4 r.p.m. (From Lever *et al.* 1971*b*.)

Fig. 2. Rolling response of newts as a function of helium pressure. The oxygen partial pressure was 1 ATA. Other conditions as for Fig. 1. (From Lever *et al.* 1971*b*.)

Fig. 3. Rolling response of newts as a function of neon pressure. Conditions as for Fig. 2. (From Lever *et al.* 1971*b*).

Fig. 4. Rolling response of newts in the presence of 34 atm nitrogen when the total pressure was raised with helium. Conditions as for Fig. 2. (From Lever *et al.* 1971*b*.)

pression with helium. We found not only that the anaesthesia was antagonized in the most spectacular manner, but also that the lethal threshold was raised significantly (Table 1).

To quantify this effect newts were anaesthetized with 34 atm nitrogen at room temperature (20 ± 1 °C). They showed nearly complete loss of ability to follow the revolving drum, but when the pressure was further increased with helium this ability was almost completely restored by 140 atm (Fig. 4). This remarkable result is of considerable theoretical interest

Table 1. *Experiments with mice at high pressures*

Inert gas	No. of mice	Threshold pressure (atm ± S.D.) Tremor	Convulsion	Death
He	9	74 ± 8	108 ± 4	135 ± 3
Ne	6	88 ± 3	130 ± 7	144 ± 11
With anaesthetic				
He + 45 atm N_2	4	—	—	166 ± 3
He*	4	—	—	200 ± 6

P_{O_2}: 0.5–1.0 atm. Temp.: 30 ± 3 °C. Average compression rate: 1.25 atm min^{-1}. (From Lever *et al.* 1971*b*.) * 0.1 mg g^{-1} Na pentobarbitone.

and is possibly of practical significance. At the practical level it suggests that inert gas narcosis need never prove a limiting problem and it also means that narcotic gases may be used in breathing mixtures at very deep depths to combat hyper-excitability. Theoretically this result may be interpreted in terms of order–disorder phenomena in membrane processes (Johnson & Miller, 1970).

To demonstrate that the anaesthesia is not being antagonized by helium but truly by pressure *per se*, newts were anaesthetized in sodium pentobarbitone solution. Fig. 5 represents the partial antagonism of anaesthesia that results when the pressure is raised hydrostatically. Similar results are indicated by exploratory experiments on butanol, ether and halothane (CF_3.CHCl.Br). It might also be supposed that the reversal occurs because the anaesthetic is squeezed out of some membrane in accordance with its partial molar volume (Mullins, 1954), thus reducing its effective concentration. However this possibility is excluded by the observation that anaesthesia caused by 68 atm nitrogen (twice the normal dose) is antagonized by pressure.

We can now ask: What is the relevance of all this to work on mammals? If we compare the mean maximum pressure that mice survive, given a sufficiently slow compression, we find that mice die at pressures which correspond to a 10–15 % loss of the ability of newts to follow the revolving drum (Table 2). This result implies that death in mice at pressure is associated with muscular impairment in a vital organ, perhaps associated with failure of normal membrane activity in some excitable tissue and thus subject to amelioration by the action of narcotics. Certainly, marked effects on nerve conduction and muscle contraction have been observed in isolated preparations at around these pressures (Cattell, 1936; Fenn, 1969). The greater sensitivity of mice to high pressure could thus be due to their absolute dependence for life on rhythmic cardiac and respiratory activity.

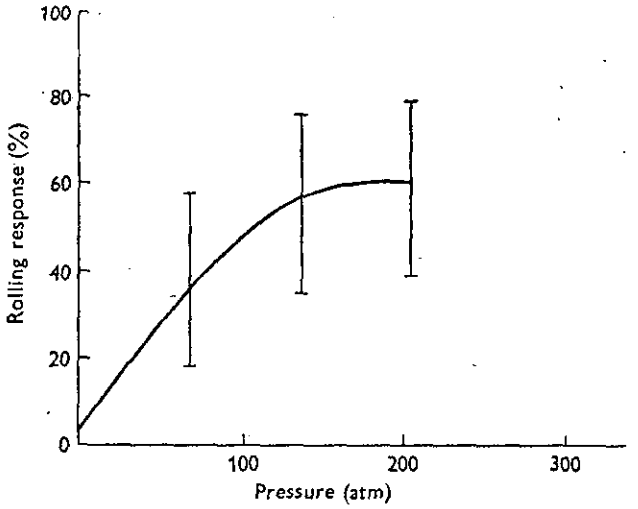


Fig. 5. Rolling response of newts as a function of hydrostatic pressure in 0.4 mg/ml sodium pentobarbitone solution. Other conditions as Fig. 1, but only 5 animals per point.

Table 2. *Comparison of the effects of pressure on mice and newts (from Lever* et al. 1971b)

	Lethal limit for mice ATA	% RR of newts at this pressure
He	159	85
Ne	(159)	90
$He–N_2$	166	92

Similar effects could also be responsible for the collapse of goats at 110–120 atm (Chouteau & Corriol, 1971) and the cardiac arrest observed in squirrel monkeys at about 135 atm (Langley, 1970). Furthermore, the observation that mice have a higher lethal pressure under conditions of low ambient temperatures (Lever *et al.* 1971*a*) may be related to a reduced demand for oxygen.

The antagonism of anaesthesia by pressure raises the interesting possibility that rather high concentrations of narcotic gases, sufficient to suppress the high-pressure convulsions (Carpenter, 1954; Brauer & Way, 1970), may be included in high-pressure breathing mixtures without causing the narcosis that would occur at lower pressures with these gases. In addition, the pressure reversal of anaesthesia throws further light on the mechanism of action of general anaesthetics, and an attempt is made to develop a semi-quantitative model with predictive value in the next section.

ANAESTHESIA AND PRESSURE

In order to appreciate the theoretical significance of the observation of the pressure reversal of anaesthesia in mice and newts, we must first consider the current physical theories of anaesthesia. These seek to define the molecular nature of the site of action of anaesthetics by establishing correlations between anaesthetic potency and physical properties. Recent studies have pointed to hydrophobic regions as the site of action of anaesthetics, and have lent little support to the aqueous phase or hydrate theories (Miller, Paton & Smith, 1965; Eger, Lundgren, Miller & Stevens, 1969; Miller, Paton, Smith & Smith, 1971).

The correlation, originally proposed by Meyer and Overton, which links anaesthetic potency with olive oil solubility holds over a dose range covering four orders of magnitude with a remarkable degree of accuracy (Fig. 6). In its most modern form the theory states that 'narcosis commences when any chemically indifferent substance has attained a certain molar concentration in the cell' (Meyer, 1937). In one sense the theory is not a theory, for it offers no explanation for the occurrence of anaesthesia at such a critical concentration. However, several attempts have been made to develop the theory mechanistically on the lines that anaesthetic molecules act by modifying the dimensions of lipid regions of membranes (e.g. Mullins, 1954; Schneider, 1968). This means that instead of the anaesthetic concentration in the lipid at equi-anaesthetic dose being constant, the product of concentration and partial molar volume of anaesthetic in lipid is, so that anaesthesia occurs at constant volume fraction rather than constant mole fraction (the critical volume model). It has always been difficult to differentiate these two versions of the lipid theory because the partial molar volumes of anaesthetics vary over such a narrow range. The volume fraction version of the theory (critical volume model) however may be very easily extended to account for pressure reversal for we can see immediately that if anaesthesia occurs when the volume of the membrane is expanded then pressure may antagonize the anaesthesia by restoring the volume. Of course any model in which increase in volume occurs would make the same qualitative prediction. Fortunately, however, it is possible to test the model in a semi-quantitative and more rigorous manner, as follows (Lever *et al.* 1971*b*; Miller & E. B. Smith, 1971).

First of all we need some estimate of the compressibility of the membrane. It is possible to estimate this by examining the correlation of anaesthetic potency with solubility in a series of simple solvents of graded solvent power, as measured by the solubility parameter δ. If we do this for the gaseous anaesthetics we find the best correlation is for solvents of solubility

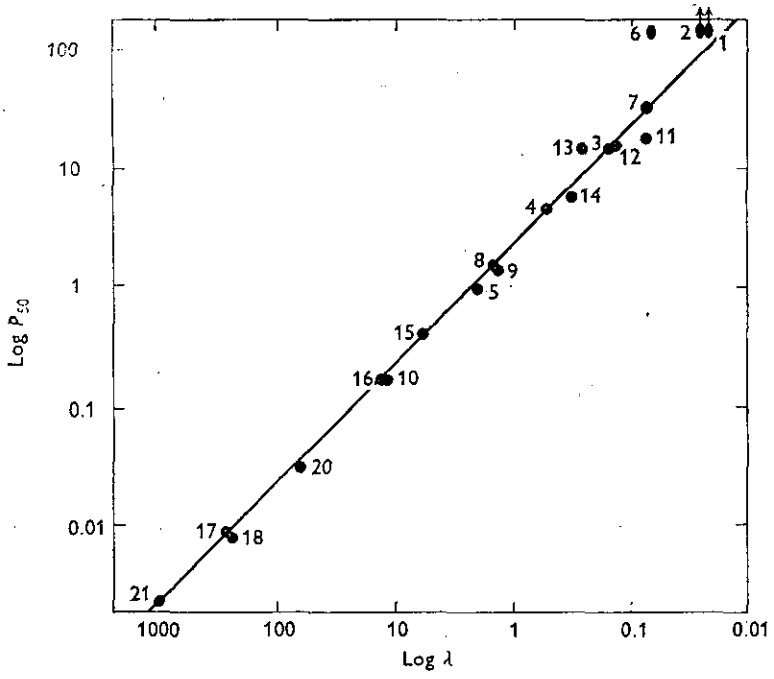


Fig. 6. Correlation of anaesthetic pressure (log P_{50}) for mice with olive oil/gas partition coefficient (log λ) at 37 °C. The line is of unit slope. Key: 1, He; 2, Ne; 3, Ar; 4, Kr; 5, Xe; 6, H_2; 7, N_2; 8, N_2O; 9, C_2H_4; 10, cC_3H_6; 11, CF_4; 12, C_2F_6; 13, C_3F_8; 14, SF_6; 15, CCl_2F_2; 16, $CHFCl_2$; 17, $CHCl_3$; 18, Halothane; 20, Ether; 21, Methoxyfluorane.

parameter around 9–10 (calories $cm^{-3})^{\frac{1}{2}}$, e.g. benzene (Miller *et al.* 1965, 1971). This value of the solvent power may be used to estimate other physical properties. Thus for a Van der Waals fluid

$$\delta^2 = \left(\frac{\partial E}{\partial V}\right)_T = T\left(\frac{\partial P}{\partial T}\right)_V = T.\frac{\alpha}{\beta},$$

where α is the coefficient of thermal expansion, β the coefficient of isothermal compressibility, E the internal energy, V the volume, P the pressure and T the absolute temperature. For a solvent of $\delta = 9$ (calories $cm^{-3})^{\frac{1}{2}}$, changing units gives $\delta = 3320$ atm, whence $\alpha/\beta = 11$ atm deg^{-1}. Thus we may estimate the compressibility of the site of action by assuming a reasonable value for α. If we assume $\alpha \approx 0.5 \times 10^{-3}$ deg^{-1} then β is estimated as $\approx 5 \times 10^{-5}$ atm^{-1}. (For benzene at 25 °C $\alpha = 1.2 \times 10^{-3}$ deg^{-1} and $\beta = 9 \times 10^{-5}$ atm^{-1}; for olive oil at 15 °C $\alpha = 0.7 \times 10^{-3}$ deg^{-1} and $\beta = 6 \times 10^{-5}$ atm^{-1} (International Critical Tables, 1926; Forsythe, 1956).) The partial molar volumes ($\bar{V}_2$) of gaseous anaesthetics in non-polar

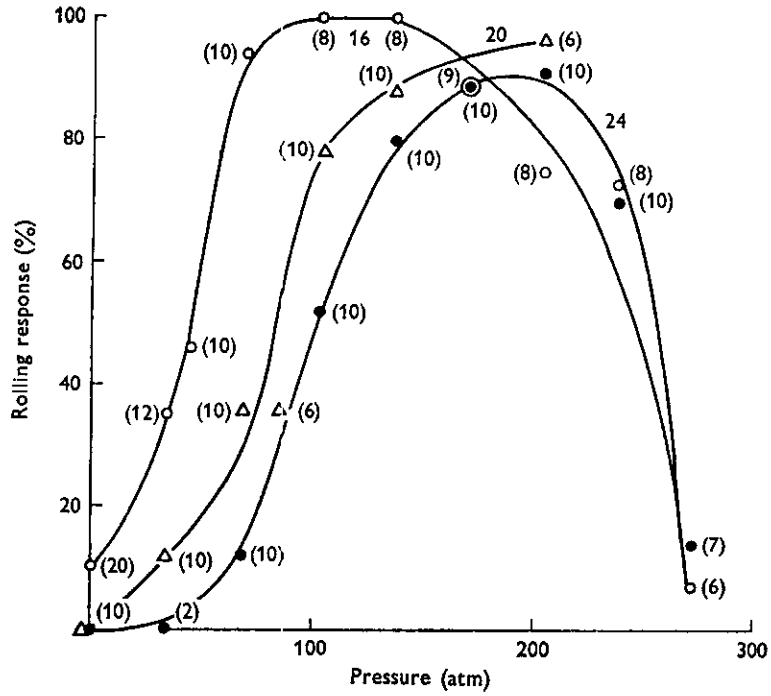


Fig. 7. Rolling response of newts as a function of helium pressure when anaesthetized with ○ 16 psia (1.09 ATA), △ 20 psia (1.36 ATA) and ● 24 psia (1.63 ATA) N_2O. Figures in parentheses are number of animals. Other conditions as Fig. 2 (psia = pounds per square inch absolute).

solvents are generally in the range 50–100 cm^3 (Walkley & Jenkins, 1968) and the calculated critical concentration for anaesthesia is $\approx$ 0.05 M, giving an expansion of the order of $\frac{1}{2}$%. Using the estimated value of β, the pressure required to nullify this expansion can now be calculated to be of the order of 100 atm. This is broadly consistent with the experimental findings presented earlier.

The order-of-magnitude predictions of the model are thus satisfactory. The model also predicts a relationship between pressure and anaesthetic dose, and recently we have been testing these predictions of the model by determining the partial pressure of various anaesthetic gases required to anaesthetize newts at different ambient pressures, helium being used to transmit pressure just as in the results already quoted for nitrogen. Results for nitrous oxide are given in Fig. 7 (Miller & R. A. Smith, 1971). Let us assume anaesthesia occurs at constant percentage expansion of some membrane, presumably synaptic.

$$\% \text{ expansion} = \frac{\overline{V}_2 . x_2 . P_a}{V_m} \times 100,$$

where $\overline{V}_2$ is the partial molar volume of the anaesthetic in that membrane and x_2 is its corresponding mole fraction solubility. V_m is the molar volume of the membrane and P_a the partial pressure of anaesthetic. In the case when $P_a = P_{50}$, the partial pressure of anaesthetic required to anaesthetize 50% of a group of animals (ED_{50}), the percentage volume expansion will be a constant for general anaesthetics according to this model. If $P_a > P_{50}$ the extra expansion may be offset by raising the total pressure with helium. The percentage compression will be given by $(\beta.P_T.100)$, where P_T is the total absolute pressure and β has its previous meaning. At any combination of P_a and P_T that gives the ED_{50} expansion we have

$$(P_a - P_{50})\frac{\overline{V}_2.x_2}{V_m} = \beta.P_T.$$

Since the ED_{50} expansion is assumed by the critical volume model to be a constant for all volatile anaesthetics we may make the substitution

$$\overline{V}_2.x_2.P_{50} = \text{constant} = B,$$

whence

$$P_a/P_{50} = \frac{V_m\beta}{B}P_T + 1.$$

Thus a plot of P_a/P_{50} *vs.* P_T should give a straight line for all general anaesthetics, since the constants in the equation are independent of the anaesthetic. (This treatment neglects the small additional expansion caused by helium, the corrections for gas imperfections and failures of Henry's law.) However, for such a plot the intercept when $P_T = 0$ is not at $P_a/P_{50} = 1$ in all cases because the compression at P_{50} has been neglected. The deviation will be more marked the greater P_{50} (*cf.* N_2) and it provides a method of obtaining 'true' ED_{50}'s independent of pressure. To allow for this compression we must include a term $(P_{50}+1)\beta$. Thus a plot of P_a/P_{50} against $[P_T-(P_{50}+1)]$ reduces the data for newts anaesthetized with N_2, N_2O, CF_4 and SF_6 to a single line (Fig. 8).

The only quantitative data for pressure reversal of general anaesthesia in mammals is that of Halsey & Eger (1971) for nitrous oxide on mice in the presence of various pressures of helium. Fig. 9 shows that their data may be successfully treated by the constant volume model, although the slope of the resultant plot is less than that for newts. Most of this difference in slopes may be assigned to the difference in P_{50} (0.75 ATA for newts at 30 °C and 1.5 ATA for mice). The remaining discrepancy appears not to be related to temperature and may reflect a real difference in the properties of the site of action of anaesthetics in mice and newts.

The evidence above provides strong support for the model and, further-

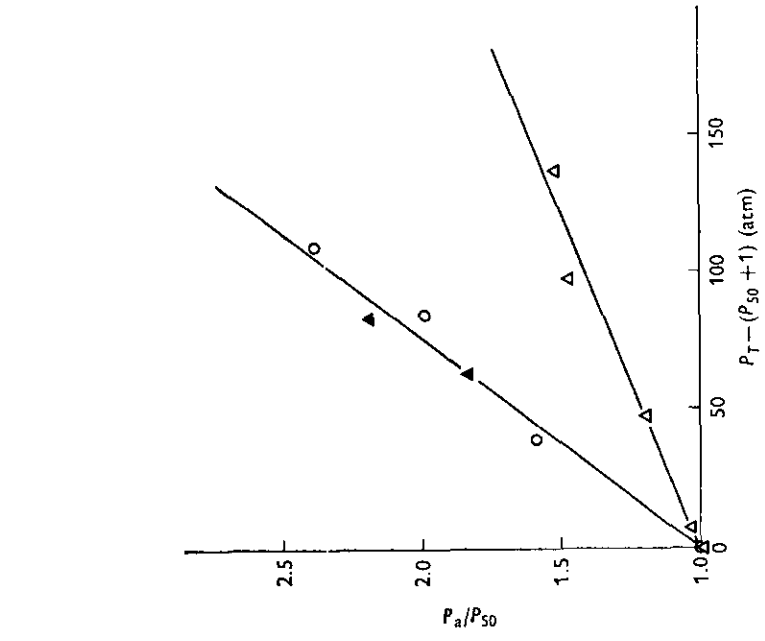


Fig. 9. Same plot as Fig. 8. Key: ○ N_2O for newts at 20 °C; ▲ N_2O for newts at 30 °C; △ N_2O for mice (Halsey & Eger, 1971).

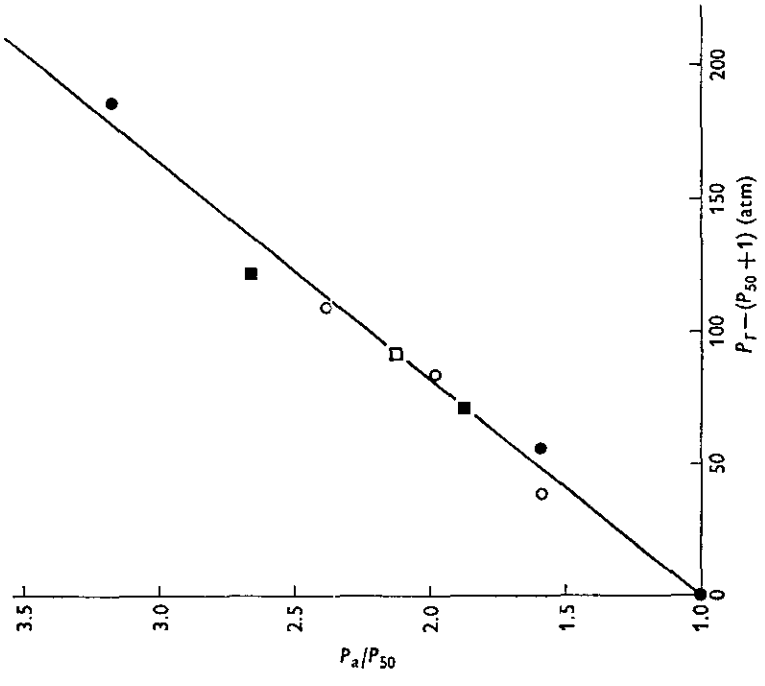


Fig. 8. Plot of P_a/P_{50} (inert gas pressure ED_{50} pressure) against total pressure (P_T) less ($P_{60}+1$) required to restore response to 50 % of animals in groups of about 10 newts at 20 °C. Key: ● N_2; ○ N_2O; □ CF_4; ■ SF_6.

more, it predicts that because the expansion caused by the dissolved gas will be more than offset by the compression of pressure *per se*, helium and neon will not be anaesthetics; as indeed is observed. For hydrogen the model predicts a situation where the gas-induced expansion is approximately balanced by pressure. This seems consistent with the observed anaesthetic pressure of hydrogen (Brauer & Way, 1970), which is much higher than predicted by the simple solubility (Meyer–Overton) model (Miller *et al.* 1971; Miller & E. B. Smith, 1971). Conceivably, the model may be generalized to account for high pressure excitability, which might be caused through membrane compression. However, insufficiently accurate data are available to test the latter hypothesis.

CONCLUSIONS

The success of the critical volume model is remarkable considering its simplicity, and it clearly provides a useful predictive framework. The fact that it is based on the behaviour of a non-polar solute analogue suggests that the inert gas molecules are acting in the hydrocarbon region of a bilayer membrane, which should be sufficiently thick ($\approx$ 30–40 Å) to appear to a gas molecule (3–6 Å) as an extensive phase, even though it is only two lipid molecules across. How anaesthesia results from the disturbance in the membrane is still an open question. It is interesting to speculate that the profound effects which occur (high pressure excitability and anaesthesia) may be due to the disturbance of proteins associated with the membrane, if the volume of the lipid bilayer is changed by compression or expansion (respectively) by a calculated $\frac{1}{2}$–1 % or more. From this point of view it may be noted that the luciferase-mediated light reaction of luminous bacteria is suppressed by both pressure and anaesthetics, although the two agents together are antagonistic (Johnson, Eyring & Polissar, 1954). Furthermore, Ebbecke (1936) noted several similarities between the effects of pressure (mechanonarkose) and of anaesthetics (chemonarkose). Studies on phospholipid membranes (Johnson & Bangham, 1969) are consistent with a mechanism involving an increase in volume of the membrane, equivalent to an increase in disorder or freedom of movement of the lipid molecules, and the interaction of anaesthetics and pressure in these membranes parallels that in newts (Johnson & Miller, 1970). Evidence from nuclear magnetic resonance studies shows that anaesthetics have a 'fluidizing' effect on erythrocyte, synaptosome, myelin and vagus nerve membranes (Metcalfe & Burgen, 1968; Metcalfe, Seeman & Burgen, 1968). An expansion caused by anaesthetics in erythrocyte membranes has been directly observed (Roth & Seeman, 1971).

Thus the basis of the critical volume model appears to be well founded. Its implications under hyperbaric conditions deserve further study.

Much of the work reported here was carried out in an interdisciplinary group at Oxford formed between Professor W. D. M. Paton of the Pharmacology Department and Dr E. B. Smith of the Physical Chemistry Laboratory. Part of the work was sponsored by the Office of Naval Research, Physiological Branch, Washington. Some of the previously unpublished data were obtained by Mr R. A. Smith.

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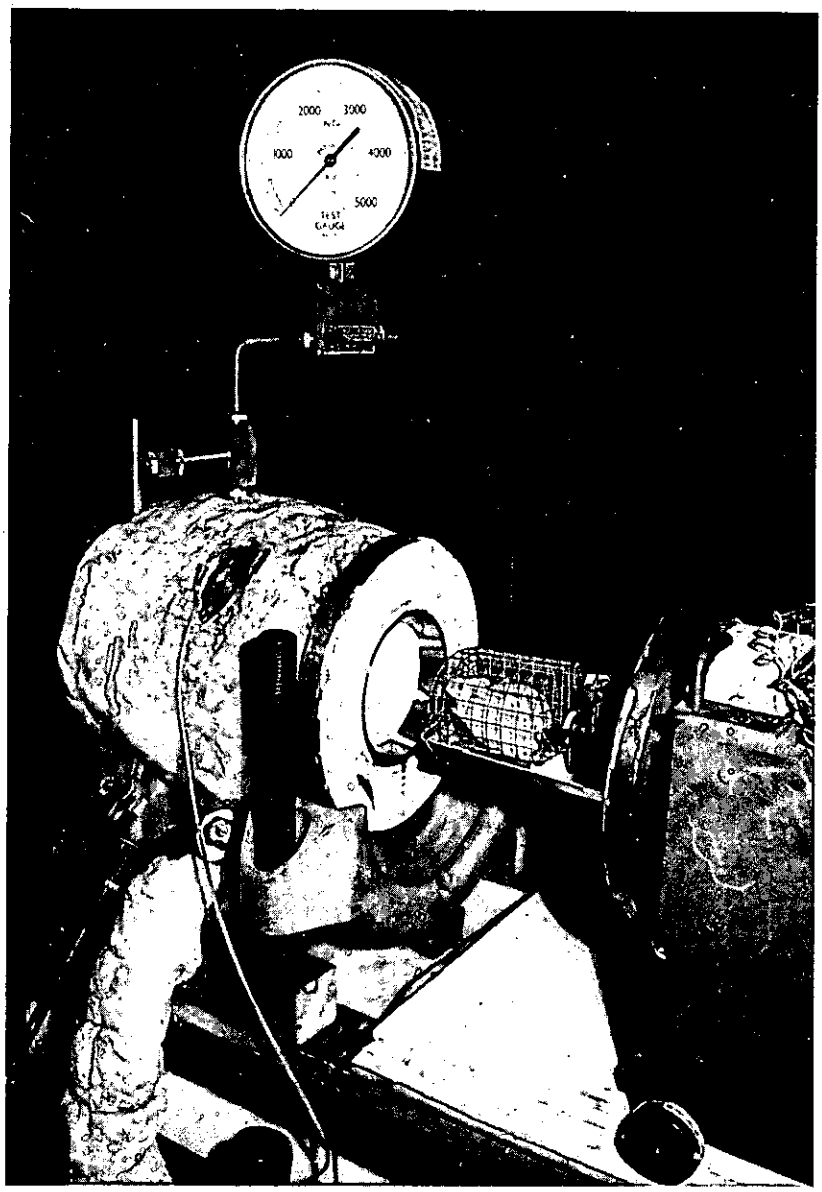
PLATE I



High-pressure chamber being used for exposure of two mice to pressures up to 300 atm. The fan is required to ensure adequate gas mixing and CO_2 removal at the soda lime tray. The chamber is maintained at 30–32 °C by water circulating within the outer jacket. Sealing is by means of a Grayloc metal–metal seal.

(*Facing p.* 376)

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PREMIER MÉMOIRE

SUR

LA RESPIRATION DES ANIMAUX,

PAR MM. SEGUIN ET LAVOISIER.

LA respiration est une des fonctions les plus importantes de l'économie animale, et en général elle ne peut être quelque temps suspendue sans que la mort n'en soit une suite inévitable. Cependant, jusqu'à ces derniers temps, on a complettement ignoré quel est son usage, quels sont ses effets : et tout ce qui est relatif à la respiration étoit au nombre de ces secrets que la nature sembloit s'être réservés.

Le retard de nos connoissances sur un objet aussi important, tient à ce qu'il existe un enchaînement nécessaire dans la suite de nos idées, un ordre indispensable dans la marche de l'esprit humain ; à ce qu'il étoit impossible de rien savoir sur ce qui se passe dans la respiration avant qu'on eût reconnu :

1°. Que le calorique (matière de chaleur) est un principe constitutif des fluides (1), et que c'est à ce principe qu'ils doivent leur état d'expansibilité, leur élasticité, et plusieurs autres des propriétés que nous leur connoissons.

(1) Sous ce nom générique, nous comprenons les *Airs* et les *Gaz*.

2°. Que l'air de l'atmosphère est un composé de deux fluides aëriformes, savoir, d'un quart environ d'air vital, et de trois quarts de gaz azote.

3°. Que la base de l'air vital, l'oxigène, est un principe commun à tous les acides, et que c'est lui qui constitue leur acidité.

4°. Que le gaz acide carbonique (air fixe) est le résultat de la combinaison d'environ 72 parties, en poids, d'oxigène, et de 28 parties de carbone (charbon pur).

5°. Qu'il entre moins de calorique dans la composition d'un volume donné de gaz acide carbonique, que dans un pareil volume d'air vital, et que c'est par cette raison qu'il se dégage du calorique pendant la combustion du carbone, c'est-à-dire pendant la conversion de l'air vital en gaz acide carbonique par l'addition du carbone.

6°. Enfin, que l'eau n'est point un élément, n'est point une substance simple, comme le croyoient les anciens ; mais qu'elle est composée de 14,338 parties d'oxigène, et de 85,668 d'hydrogène (1).

M. Lavoisier, l'un de nous, a établi toutes ces vérités dans une suite de mémoires qui font partie du recueil de l'Académie ; et maintenant que ces vérités ont reçu la sanction du temps, qu'elles se trouvent confirmées par l'assentiment de presque tous les physiciens et les chimistes de l'Europe, nous pouvons dire avec confiance qu'il n'en existe pas en chimie, qui soient fondées sur des preuves plus évidentes

Enfin il étoit impossible de soumettre à des expériences précises les effets de la respiration avant qu'on eût acquis des moyens simples, faciles et expéditifs de faire l'analyse

(1) Nous nous servons ici du résultat indiqué par MM. Fourcroy, Séguin et Vauquelin, parce qu'il dérive d'une des expériences les plus exactes qui aient été faites en chimie.

de l'air ; et c'est un service que M. Seguin vient de rendre à la chimie (1).

Boile, Hales, Black et Priesley, sont les premiers qui se soient apperçus que la respiration exerce une action marquée sur l'air de l'atmosphère ; qu'elle en diminue le volume, qu'elle en change la nature, et qu'en un assez court intervalle de temps, le fluide qui sert à cette fonction, perd la propriété d'entretenir la vie des animaux.

Sans trop se rendre compte de ce qui se passoit dans ce genre d'expérience, les chimistes sectateurs de la doctrine de Sthal, essayèrent d'en expliquer les résultats : ils y parvinrent avec cette facilité qu'on leur connoît ; c'est-à-dire, à l'aide de leur principe ordinaire, le phlogistique qui, comme un Protée, peut se prêter à tout et prendre toutes les couleurs, comme toutes les formes. Supposant donc que, pendant la respiration, il s'exhaloit des poumons des animaux une certaine quantité de phlogistique, les disciples de Sthal admirent la phlogistication de l'air par la respiration, comme ils avoient admis la phlogistication par la combustion, par l'oxidation des métaux, etc. et comme les produits de ces différentes opérations leur parurent identiques, ils y trouvèrent de nouveaux motifs de conclure que le phlogistique étoit un être identique dans les trois règnes de la nature.

Des expériences de comparaison que M. Lavoisier entreprit bientôt après, lui firent connoître les principaux effets et les différens produits de la respiration, de la combustion, de l'oxidation, etc. et le mirent en état d'apprécier le degré d'analogie qui existe entre ces diverses opérations. Il fit voir que dans toutes il y a décomposition de l'air vital contenu dans l'air atmosphérique, et dégage-

(1) Mémoire sur l'endiométrie. Annales de chimie, tom. 9, page 293.

ment

ment d'une portion de son calorique spécifique ; que dans toutes, il reste après le lavage dans l'alcali, (alcali caustique) un résidu identique, le gaz azote, qui n'est point un produit de l'opération, mais qui est une partie constituante de l'air atmosphérique.

Il annonça ensuite, en 1777, que la respiration est une combustion lente d'une portion de carbone que contient le sang, et que la chaleur animale est entretenue par la portion de calorique qui se dégage au moment de la conversion de l'air vital de l'atmosphère en gaz acide carbonique, comme il arrive dans toute combustion de carbone.

Les expériences que publièrent, en 1780, MM. de la Place et Lavoisier (1), non-seulement confirmèrent ces énoncés, mais elles offrirent encore un résultat tout-à-fait inattendu, et dont il étoit impossible alors de sentir toute l'importance. Ces deux physiciens reconnurent qu'il se dégage des animaux, dans un temps donné, une quantité de calorique plus grande que celle qui devroit résulter de la quantité de gaz acide carbonique qui se forme dans un temps égal, par leur respiration.

Enfin, en 1785, M. Lavoisier crut pouvoir annoncer, dans un mémoire publié dans le recueil de la société de Médecine, que très-probablement la respiration ne se borne pas à une combustion de carbone, mais qu'elle occasionne encore la combustion d'une partie de l'hydrogène contenu dans le sang ; et conséquemment que la respiration opère, non-seulement une formation de gaz acide carbonique, mais encore une formation d'eau ; ce qui explique parfaitement bien le phénomène observé par MM. de la Place et Lavoisier.

M. Seguin donna de nouveaux développemens à cette théorie, et la confirma par de nouvelles expériences dans

(1) Mémoires de l'académie des sciences, année 1780, page 355.

un mémoire qu'il lut à la société de Médecine. Il y présenta un extrait des recherches de MM. Priesley, Crawford, Hamilton, etc. sur cet objet, et y exposa les conséquences qu'on pouvoit en déduire.

Tel étoit l'état de nos connoissances à l'instant où nous avons formé le plan d'un travail très-étendu, sur presque toutes les parties de l'économie animale. Nous allons présenter dans ce premier mémoire les principaux résultats des expériences que nous avons faites sur la respiration.

En partant des connoissances acquises, et en nous réduisant à des idées simples, que chacun puisse facilement saisir, nous dirons d'abord, en général, que la respiration n'est qu'une combustion lente de carbone et d'hydrogène, qui est semblable en tout à celle qui s'opère dans une lampe ou dans une bougie allumée ; et que sous ce point-de-vue, les animaux qui respirent sont de véritables corps combustibles qui brûlent et se consument.

Dans la respiration, comme dans la combustion, c'est l'air de l'atmosphère qui fournit l'oxigène et le calorique ; mais comme dans la respiration, c'est la substance même de l'animal, c'est le sang qui fournit le combustible, si les animaux ne réparoient pas habituellement par les alimens, ce qu'ils perdent par la respiration, l'huile manqueroit bientôt à la lampe ; et l'animal périroit comme une lampe s'éteint, lorsqu'elle manque de nourriture.

Les preuves de cette identité d'effets entre la respiration et la combustion se déduisent immédiatement de l'expérience. En effet l'air qui a servi à la respiration, ne contient plus, à la sortie du poumon, la même quantité d'oxigène ; il renferme non-seulement du gaz acide carbonique, mais encore beaucoup plus d'eau qu'il n'en contenoit avant l'inspiration. Or, comme l'air vital ne peut se convertir en gaz acide carbonique que par une addition de carbone ; qu'il

ne peut se convertir en eau que par une addition d'hydrogène ; que cette double combinaison ne peut s'opérer sans que l'air vital ne perde une partie de son calorique spécifique ; il en résulte que l'effet de la respiration est d'extraire du sang une portion de carbone et d'hydrogène, et d'y déposer à la place une portion de son calorique spécifique, qui, pendant la circulation, se distribue avec le sang dans toutes les parties de l'économie animale, et entretient cette température à-peu-près constante, qu'on observe dans tous les animaux qui respirent.

On diroit que cette analogie, qui existe entre la respiration et la combustion, n'avoit point échappé aux poétes, ou plutôt aux philosophes de l'antiquité dont ils étoient les interprêtes et les organes. Ce feu dérobé du ciel, ce flambeau de Prométhée ne présente pas seulement une idée ingénieuse et poétique ; c'est la peinture fidèle des opérations de la nature, du moins pour les animaux qui respirent : on peut donc dire avec les anciens, que le flambeau de la vie s'allume au moment où l'enfant respire pour la première fois, et qu'il ne s'éteint qu'à sa mort.

En considérant des rapports si heureux, on seroit quelquefois tenté de croire, qu'en effet les anciens avoient pénétré plus avant que nous ne le pensons, dans le sanctuaire des connoissances, et que la fable n'est véritablement qu'une allégorie, sous laquelle ils cachoient les grandes vérités de la médecine et de la physique.

Tout ce que nous avons à dire en ce moment sur la respiration, n'est que le développement de l'idée principale que nous venons d'énoncer. Nous avons commencé ce mémoire par où, peut-être, nous aurions dû le finir, par la conséquence. Mais nous avons pensé, qu'au risque même de nous répéter, il pourroit être utile d'offrir, dès le commencement, au lecteur, le fil qui doit le conduire. Le

voyageur est moins sujet à s'égarer, lorsqu'il voit devant lui le terme auquel il se propose d'arriver.

C'est sur des cochons d'inde que nous avons d'abord opéré. Ces animaux sont doux, la nature ne leur a donné aucun moyen de nuire. Ils sont d'une constitution robuste, faciles à nourrir ; ils supportent long-temps la faim et la soif ; enfin, ils sont assez gros pour produire en très-peu de temps des altérations sensibles dans l'air qu'ils respirent.

La quantité d'air vital qu'ils consomment par heure, est de 40 à 50 pouces cubiques, suivant leur force et leur grosseur : mais comme le gaz acide carbonique est pour eux, ainsi que pour presque tous les animaux, un poison mortel, qu'ils ne peuvent respirer, même en médiocre quantité, sans éprouver des accidens funestes, il est nécessaire, pour continuer long-temps les expériences sur le même animal, sans qu'il en souffre, d'absorber le gaz acide carbonique à mesure qu'il se forme. Pour remplir cet objet, nous commencions par faire passer sous une cloche de verre, une quantité connue d'air vital ; nous y introduisions ensuite le cochon d'inde, en le faisant passer à travers l'eau : dès qu'il étoit sous la cloche, nous le soulevions et nous le soutenions dans l'air qu'elle contenoit, à l'aide d'une espèce de sibille de bois, montée sur trois pieds et recouverte d'une toile de crin : les pieds de ce support étoient assez longs pour que l'animal fut soutenu à six ou huit pouces au-dessus de la surface de l'eau.

On conçoit que la sibille, en passant ainsi à travers de l'eau, devoit s'en remplir : nous la vuidions avec un siphon ; après quoi nous y introduisions de l'alcali au moyen d'un entonnoir adapté à un tube recourbé. Ces opérations se font avec facilité, quand on y est habitué.

Pour plus de sûreté, nous placions encore entre les trois

pieds du support une capsule qui nageoit sur la surface de l'eau, et que nous remplissions également d'alcali. Avec ces précautions le gaz acide carbonique étoit aussi-tôt absorbé que formé, et l'animal n'étoit pas plus incommodé, que s'il eût respiré dans l'air libre. Si l'expérience dure long-temps, plusieurs jours par exemple, il faut remplacer par des quantités connues d'air vital, celui qui est absorbé par la respiration de l'animal, ou plutôt qui est employé à former du gaz acide carbonique et de l'eau. On doit avoir également soin de renouveller l'alcali, lorsqu'il approche d'être saturé d'acide carbonique.

On sait que la combustion, toutes choses égales d'ailleurs, est d'autant plus rapide que l'air dans lequel elle s'opère, est plus pur. Ainsi, par exemple, il se consomme dans un temps donné beaucoup plus de charbon ou de tout autre combustible, dans l'air vital, que dans l'air de l'atmosphère. On avoit toujours pensé qu'il en étoit de même de la respiration ; qu'elle devoit s'accélérer dans l'air vital, et qu'alors il devoit se dégager soit dans le poumon, soit dans le cours de la circulation une plus grande quantité de calorique. Mais l'expérience a détruit toutes ces opinions qui n'étoient fondées que sur l'analogie. Soit que les animaux respirent dans l'air vital pur, soit qu'ils respirent dans ce même air, mêlangé avec une proportion plus ou moins considérable de gaz azote, la quantité d'air vital qu'ils consomment est toujours la même, à de très-legères différences près. Il nous est arrivé plusieurs fois, de tenir un cochon d'inde pendant plusieurs jours, soit dans l'air vital pur, soit dans un mêlange de quinze parties de gaz azote et d'une d'air vital, en entretenant constamment les mêmes proportions ; l'animal dans les deux cas est demeuré dans son état naturel ; sa respiration et sa circulation ne paroissoient pas sensiblement, ni accélérées, ni retardées ; sa chaleur étoit égale ; et il

avoit seulement, lorsque la proportion de gaz azote devenoit trop forte, un peu plus de disposition à l'assoupissement.

M. Lavoisier avoit déjà annoncé que le gaz azote, contenu dans l'atmosphère, n'éprouvoit aucun changement pendant la respiration, et qu'il ressortoit du poumon en même quantité qu'il y étoit entré. Nous avons cru devoir constater ce fait par des expériences très-rigoureuses, et nous nous sommes assurés que réellement il n'y a ni dégagement, ni absorption de gaz azote pendant la respiration. Il y avoit, d'après cela, lieu de présumer qu'on pouvoit substituer au gaz azote qui entre dans la composition de l'air de l'atmosphère, un volume égal d'un gaz quelconque, pourvu qu'il ne fut ni acide, ni alcali, et qu'il n'eut aucune qualité nuisible. L'expérience a encore confirmé pleinement cette conjecture.

Nous avons essayé d'introduire des cochons d'inde sous des cloches de verre, remplies d'un mêlange d'air vital et de gaz hydrogène pur, à peu près dans les proportions en volume, qui existent entre l'air vital et le gaz azote dans l'air de l'atmosphère. Ils y ont demeuré long-temps sans paroître souffrir ; et ce n'est qu'au bout de huit ou dix heures qu'ils ont donné des signes de mal aise. Le gaz hydrogène n'a paru avoir éprouvé aucune diminution, et il est ressorti de leur poumon à peu près tel qu'il y étoit entré.

Nous répéterons une dernière fois, que dans toutes ces expériences, il est nécessaire d'absorber, au moyen de l'alcali, le gaz acide carbonique à mesure qu'il se forme ; qu'autrement l'animal périroit, en peu de temps, par une suite de l'action irritante que le gaz acide carbonique exerce sur le poumon.

Ces premières expériences donnoient déjà des idées générales sur la respiration : nous avions même entrevu qu'elle

s'accéléroit pendant la digestion, et que les animaux consommoient alors une plus grande quantité d'air. Nous avions également apperçu que le mouvement et l'agitation augmentoient encore ces effets : mais nous étions loin encore du but que nous nous étions proposé d'atteindre, et d'ailleurs après avoir opéré sur des animaux, nous desirions de faire des applications plus particulières à ce qui se passe dans la respiration humaine.

Quelque pénibles, quelque désagréables, quelque dangéreuses même, que fussent les expériences auxquelles il falloit se livrer, M. Seguin a desiré qu'elles se fissent toutes sur lui même. Nous les avons répétées un grand nombre de fois, et la précision des résultats a presque toujours été au-delà de nos espérances. L'Académie a sous les yeux une partie des appareils dont nous nous sommes servis. Nous en donnerons la description détaillé dans un autre mémoire.

Il résulte des expériences auxquelles M. Seguin s'est soumis, qu'un homme à jeun, dans un état de repos et dans une température de 26 degrés de thermomètre de mercure, divisé en 80 parties, consomme par heure 1210 pouces cubes d'air vital : que cette consommation augmente par le froid, et que le même homme également à jeun et en repos, mais dans une température de 12 degrés seulement, consomme par heure 1344 pouces d'air vital.

Pendant la digestion, cette consommation s'élève à 18 ou 19 cent pouces.

Le mouvement et l'exercice augmentent considérablement toutes ces proportions. M. Seguin, étant à jeun et ayant élevé, pendant un quart d'heure, un poids de 15 livres à une hauteur de 613 pieds ; sa consommation d'air, pendant ce temps, a été de 800 pouces, c'est-à-dire de 3200 pouces par heure.

Enfin le même exercice fait pendant la digestion, a porté à 4600 pouces par heure la quantité d'air vital consommé.

Les efforts que M. Seguin avoit faits dans cet intervalle, équivaloient à l'élévation d'un poids de 15 livres à une hauteur de 650 pieds pendant un quart-d'heure.

Dans toutes ces expériences, la température du sang demeure assez constamment la même, du moins à quelques fractions de degrés près. Mais le nombre des pulsations des artères, et celui des inspirations varient d'une manière très-remarquable. Nous sommes parvenus à cet égard, à constater deux lois de la plus haute importance. La première, c'est que l'augmentation du nombre des pulsations est assez exactement, en raison directe de la somme des poids élevés à une hauteur déterminée ; pourvu toutefois que la personne soumise aux expériences ne porte pas ses efforts trop près de la limite de ses forces ; parce qu'alors elle est dans un état de souffrance et sort de l'état naturel. La seconde, c'est que la quantité d'air vital consommé est, toutes choses égales d'ailleurs, lorsque la personne ne respire qu'aussi souvent que le besoin l'exige, en raison composée des inspirations et des pulsations, c'est-à-dire en raison directe du produit des inspirations par les pulsations.

Nous ne parlons en ce moment que de rapports. On conçoit en effet que la consommation absolue doit varier considérablement dans différens individus, suivant leur âge, leur état de vigueur et de santé, suivant qu'ils ont plus ou moins contracté l'habitude des travaux pénibles : mais il n'en est pas moins vrai qu'il existe pour chaque personne une loi qui ne se dément pas, lorsque les expériences sont faites dans les mêmes circonstances et à des intervalles de temps peu éloignés. Ces lois sont même assez constantes pour qu'en appliquant un homme à un exercice pénible et en observant l'accélération qui en résulte dans le cours de la circulation, on puisse en conclure à quel poids élevé

élevé à une hauteur déterminée, répond la somme des efforts qu'il a faits pendant le temps de l'expérience.

Ce genre d'observations conduit à comparer des emplois de force entre lesquels il sembleroit n'exister aucun rapport. On peut connoître, par exemple, à combien de livres, en poids, répondent les efforts d'un homme qui récite un discours, d'un musicien qui joue d'un instrument. On pourroit même évaluer ce qu'il y a de mécanique dans le travail du philosophe qui réfléchit, de l'homme de lettres qui écrit, du musicien qui compose. Ces effets considérés comme purement moraux, ont quelque chose de physique et de matériel qui permet, sous ce rapport, de les comparer avec ceux que fait l'homme de peine. Ce n'est donc pas sans quelque justesse que la langue françoise a confondu sous la dénomination commune de *travail*, les efforts de l'esprit comme ceux du corps; le travail du cabinet et le travail du mercenaire.

Il résulte de tout ce que nous venons de dire que la quantité d'air vital que consomment les différens individus est très-variable, et qu'elle n'est rigoureusement la même dans aucune circonstance de la vie, dans aucun des instans de la journée. Cependant, si l'on veut avoir de cette consommation moyenne, ou du moins la plus ordinaire, une idée facile à retenir, on peut l'évaluer à un pied cube ou 1728 pouces par heure; ce qui revient, pour les 24 heures, à 24 pieds cubes, et en poids, à $2^{liv.}\ 1^{onc.}\ 1^{gros.}$ Nous donnerons avec une grande exactitude, dans un prochain *mémoire*, la quantité d'acide carbonique et d'eau que cette quantité d'air forme dans le poulmon : en attendant, nous supposerons que cette quantité est de $2^{liv.}\ 5^{onc.}\ 4^{gros}$ d'acide carbonique, et de $5^{gros}\ 51^{gr.}$ d'eau.

Mais puisque l'acide carbonique est composé de 72 parties de gaz oxigène, et de 28 de charbon ; puisque l'eau est composée de 85 parties d'oxigène et de 15 d'hydrogène ou gaz inflammable ; enfin, puisqu'il se forme en $24^{h.}$ par la respiration $2^{liv.}\ 5^{onc.}\ 4^{gr.}$ d'acide carbonique, il en résulte que la respiration enlève au sang en vingt-quatre heures $10^{onc.}\ 4^{gr.}$ de carbone et $1^{onc.}\ 5^{gr.}\ 51^{gr.}$ d'hydrogène.

Tant que nous n'avons considéré dans la respiration que la seule consommation de l'air, le sort du riche et celui du pauvre étoit le même ; car l'air appartient également à tous et ne coute rien à personne : l'homme de peine qui travaille davantage, jouit même plus complettement de ce bienfait de la nature : Mais maintenant que l'expérience nous apprend que la respiration est une véritable combustion qui consume, à chaque instant, une portion de la substance de l'individu ; que cette consommation est d'autant plus grande que la circulation et la respiration sont plus accélérées, qu'elle augmente à proportion que l'individu mène une vie plus laborieuse et plus active, une foule de considérations morales naissent comme d'elles-mêmes de ces résultats de la physique. Par quelle fatalité arrive-t-il que l'homme pauvre qui vit du travail de ses bras, qui est obligé de déployer pour sa subsistance, tout ce que la nature lui a donné de forces, consomme plus que l'homme oisif, tandis que ce dernier a moins besoin de réparer ? Pourquoi, par un contraste choquant, l'homme riche jouit-il d'une abondance qui ne lui est pas physiquement nécessaire, et qui sembloit destinée pour l'homme laborieux ? Gardons-nous cependant de calomnier la nature, et de l'accuser des fautes qui tiennent, sans doute, à nos institutions sociales, et qui, peut-être, en sont inséparables. Contentons-nous de bénir la philosophie et l'humanité qui se réunissent pour nous promettre des insti-

tutions sages, qui tendront à rapprocher les fortunes de l'égalité, à augmenter le prix du travail, à lui assurer sa juste récompense; à présenter à toutes les classes de la société, et sur-tout aux classes indigentes, plus de jouissances et plus de bonheur. Faisons des vœux, sur-tout, pour que l'enthousiasme et l'exagération qui s'emparent si facilement des hommes réunis en assemblées nombreuses, pour que les passions humaines qui entraînent la multitude, si souvent contre son propre intérêt, et qui comprennent dans leur tourbillon le sage et le philosophe comme les autres hommes, ne renversent pas un ouvrage entrepris dans de si bonnes vues, et ne détruisent pas l'espérance de la patrie.

L'ordre physique, assujetti à des lois immuables, arrivé des long-temps à un état d'équilibre que rien ne peut déranger, n'est point sujet à ces mouvemens tumultueux que présente quelquefois l'ordre moral. C'est une chose vraiment admirable que ce résultat de forces continuellement variables et continuellement en équilibre, qui s'observent, à chaque pas, dans l'économie animale, et qui permettent à l'individu de se prêter à toutes les circonstances où le hasard le place. L'homme, à cet égard, a été plus favorisé, par la nature, qu'aucun des autres animaux: il vit également dans toutes les températures et dans tous les climats: son tempérament se prête au mouvement et au repos, à l'abstinence comme aux excès de nourriture: presque tous les alimens lui sont bons, soit qu'ils soient succulens, soit qu'ils ne le soient pas; soit qu'ils appartiennent à un règne ou à un autre.

Se trouve-t-il dans un climat froid? d'un côté, l'air étant plus dense, il s'en décompose une plus grande quantité dans le poumon; plus de calorique se dégage et va réparer la perte qu'occasionne le refroidissement extérieur. D'un autre côté, la transpiration diminue, il se fait moins d'évaporation, donc moins de refroidissement. Le même individu

passe-t-il dans une température beaucoup plus chaude ? l'air est plus raréfié, il ne s'en décompose plus une aussi grande quantité ; moins de calorique se dégage dans le poumon ; une transpiration abondante, qui s'établit, enlève tout l'excédent du calorique que fournit la respiration : et c'est ainsi que s'établit cette température à peu près constante de 32°, (*Thermomètre de Réaumur.*) que plusieurs quadrupèdes, et que l'homme, particulièrement, conservent dans quelque circonstance qu'ils se trouvent.

Il existe de semblables compensations qui permettent à l'homme de passer successivement, suivant ses besoins et sa volonté, d'une vie active à une vie tranquille : se tient-il dans un état d'inaction et de repos ? la circulation est lente ainsi que la respiration : il consomme moins d'air : il exhale par le poumon, moins de carbone et d'hydrogène, et, conséquemment, il a besoin de moins de nourriture.

Est-il obligé de se livrer à des travaux pénibles ? la respiration s'accélère ; il consomme plus d'air ; il perd plus d'hydrogène et de carbone, et, conséquemment, il a besoin de réparer plus souvent et davantage par la nutrition.

En rapprochant ces réflexions des résultats qui les ont précédées, on voit que la machine animale est principalement gouvernée par trois régulateurs principaux ; la respiration qui consomme de l'hydrogène et du carbone, et qui fournit du calorique ; la transpiration qui augmente ou diminue suivant qu'il est nécessaire d'emporter plus ou moins de calorique ; enfin la digestion, qui rend au sang ce qu'il perd par la respiration et la transpiration.

L'intensité de l'action de ces trois agens peut varier dans des limites assez étendues : mais il est des bornes au-delà des-

quelles les compensations ne peuvent plus avoir lieu, et c'est alors que commence l'état de maladie. Quoique cet objet semble étranger à l'Académie, et faire plus particulièrement partie du domaine de quelques autres sociétés savantes; cependant, comme les travaux dont elle s'occupe embrassent l'universalité des connoissances humaines, nous nous reprocherions d'écarter quelques considérations importantes qui se trouvent essentiellement liées au sujet que nous traitons.

Dans la course, dans la danse, dans tous les exercices violens, quelqu'accélération qu'éprouvent la respiration et la circulation, quelqu'accroissement que prenne la consommation d'air, de carbone et d'hydrogène, l'équilibre de l'économie animale n'est pas troublé, tant que les alimens, plus ou moins digérés, qui sont presque toujours en réserve dans l'étendue du canal intestinal, fournissent aux pertes : mais si la dépense qui se fait par le poumon est supérieure à la recette qui se fait par la nutrition, le sang se dépouille de plus en plus d'hydrogène et de carboue; et telle est la cause, sans doute, des maladies inflammatoires, proprement dites.

Dans ces cas, l'animal est averti du danger qu'il court, par la lassitude, par l'épuisement et par la perte de ses forces; il sent le besoin de rétablir l'équilibre dans l'économie animale, par la nourriture et par le repos. Les individus, d'un tempérament foible, en sont avertis plutôt que les autres; et c'est par cette raison que les personnes d'un tempérament robuste, sont les plus exposées aux maladies violentes.

L'effet contraire doit arriver, soit par le défaut absolu de tout mouvement, de tout exercice; soit par l'usage de certains alimens; soit enfin par un vice des organes de la nutrition ou de ceux de la respiration. La digestion, dans ces différens cas, introduisant dans le sang plus de substance que la respiration n'en peut consommer, il doit s'éta-

blir dans la masse du sang un excès de carbone ou un excès d'hydrogène ; ou de l'un et de l'autre à la fois. La nature lutte alors contre cette altération des humeurs : elle presse la circulation par la fièvre ; elle s'efforce de réparer par une respiration accélérée, le désordre qui trouble sa marche : souvent elle y parvient, sans aucun secours étranger, et alors l'animal recouvre la santé. Dans le cas contraire, il succombe, à moins que la nature ne trouve d'autres moyens de rétablir l'équilibre. C'est très-probablement ce qui se passe dans les maladies putrides, les fièvres malignes, etc. classe de maladies bien connue quant aux simptômes, mais très-peu connue quant aux causes qui les produisent ; et quant aux méthodes curatives.

On conçoit, d'après ces simples apperçus, comment l'art du médecin consiste souvent à laisser la nature aux prises avec elle-même ; comment, par la diète seule, il est possible de changer la qualité du sang, en diminuant la quantité de carbone et d'hydrogène qu'il contient : en effet alors la respiration consommant toujours, et la digestion ne fournissant plus, le sang doit alors se dépouiller de plus en plus de carbone et d'hydrogène.

On conçoit encore comment une diète trop austère et trop long-temps continuée, pourroit changer, à la longue, la nature de la maladie ; comment les purgatifs, en suspendant les fonctions de la digestion, donnent à la respiration le temps de remplir son office et d'évacuer l'excès du carbone et de l'hydrogène qui s'est accumulé dans le sang ; comment les mêmes purgatifs imprudemment administrés dans les maladies où les humeurs tendent à l'inflammation, contrarient le vœu de la nature, empêchent les organes de la digestion de rendre au sang l'hydrogène et le carbone qui lui manquent, augmentent l'inflammation et conduisent le malade à la mort.

Enfin, on concoit comment les altérations survenues à

l'air qui nous environne, peuvent être la cause de maladies endémiques, des fièvres d'hôpitaux et de prisons, comment le grand air, une respiration plus libre, un changement de genre de vie sont souvent pour ces dernières maladies, le remède le plus efficace.

Nous ne nous dissimulons pas une objection qu'on peut faire, et que nous nous sommes faite à nous-mêmes, contre la théorie que nous venons de présenter. Aucune expérience ne prononce d'une manière décisive que le gaz acide carbonique, qui se dégage pendant l'expiration, se soit formé immédiatement dans le poumon, ou dans le cours de la circulation par la combinaison de l'oxigène de l'air avec le carbone du sang. Il seroit possible qu'une partie de cet acide carbonique se formât par la digestion, qu'il fût introduit dans la circulation avec le chyle ; enfin, que parvenue dans le poumon, il fut dégagé du sang à mesure que l'oxigène se combine avec lui par une affinité supérieure.

Les expériences que nous avons déjà entreprises sur la digestion et sur la transpiration, éclairciront probablement ce doute : elles lèveront, nous l'espérons du moins, les incertitudes qui nous restent encore sur cet objet. Peut-être alors serons-nous obligés d'apporter quelques changemens à la doctrine que nous avons présentée dans ce mémoire. Ces modifications des premières idées, ne coûtent rien à ceux qui ne cherchent la vérité que pour elle-même, et sans autre desir que celui de la trouver. Nous ne nous croyons pas, au surplus, éloignés du terme, où, après avoir éliminé toutes les incertitudes, la théorie de la respiration ne laissera plus rien à desirer.

Nous terminerons ce mémoire par une réflexion consolante. Il n'est pas indispensable, pour bien mériter de

l'humanité; et pour payer son tribut à la patrie, d'être appellé à ces fonctions publiques et éclatantes, qui concourent à l'organisation et à la régénération des empires. Le physicien peut aussi dans le silence de son laboratoire et de son cabinet, exercer des fonctions patriotiques : il peut espérer par ses travaux de diminuer la masse des maux qui affligent l'espèce humaine, d'augmenter ses jouissances et son bonheur ; et n'eut-il contribué, par les routes nouvelles qu'il s'est ouvertes, qu'à prolonger de quelques années, de quelques jours même, la vie moyenne des hommes, il pourroit aspirer aussi au titre glorieux de bienfaiteur de l'humanité.

DEEP-SEA DIVING WITH SYNTHETIC GAS MIXTURES*

By ARNE ZETTERSTRÖM

Note: From Engineer Commodore Ture Zetterström, Acting Engineer General, RSN, and Surgeon Commodore Herbert Westermark, Surgeon General, RSN, we have received the following two papers on work done in the above field. The first paper was written by a son of Commodore Zetterström, Arne Zetterström, who lost his life when practising his own diving method. The second paper is written by two medical officers in the Swedish Navy who had the prerogative of being co-operators to Zetterström Jr. The two papers are accompanied by an obituary on the ingenious constructor Arne Zetterström. On account of their own worth and in order to honor the memory of the young constructor who died under so tragic circumstances, these papers are now for the first time laid before an American medical public.

(With five illustrations and three charts)

The Swedish Hydrogen Method

IN ADDITION to helium there is another gas, mentioned above, which is theoretically usable, and that is hydrogen. In September, 1943, I suggested to Swedish Navy Supply Corps to use hydrogen in deep-sea diving in such a way that there would be no risk from explosion.

Fig. 1. Breathing mask to reduce gas consumption.

Obviously, if hydrogen is to be used as a breathing gas, it must be mixed with oxygen to such an extent that the partial pressure of oxygen is sufficient for breathing. The gas mixture must also be safe from explosion. From figure 2 it can be seen that a ternary mixture of hydrogen, nitrogen, and oxygen cannot explode if the oxygen content is less than 4%. This is true regardless of the nitrogen content. Figures 3 and 4 show that such gas mixtures can be compressed and heated without any risks. If the gas contains 4% of oxygen, the partial pressure of the oxygen will not suffice until a depth of 30 meters or more has been reached. It it therefore necessary to descend to this depth with ordinary air and then change to a mixture of oxygen and hydro-

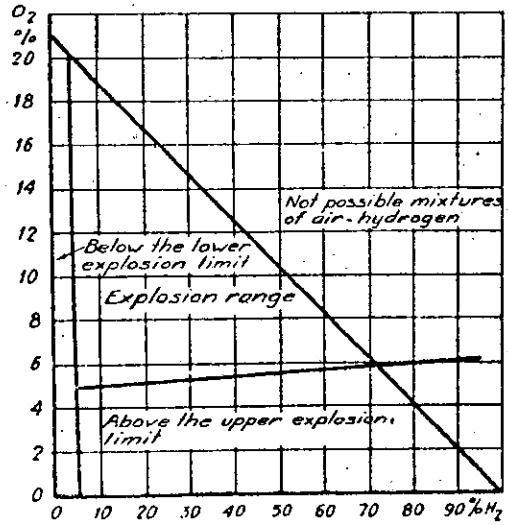

Fig. 2. Explosion intervals for the mixture hydrogen-air.

* Translation from the Swedish original published in "Teknisk Tidskrift," n:r 7, 1945. Read to the members of Svenska Teknologföreningen (The Swedish Association of Engineers and Architects, Section for Naval Architecture and Aeronautical Sciences) on November 18, 1944.

In the first section of this lecture, that was held before an audience of non-medical persons, the author expounds the essential features of the physiology of diving and gives an account for the American helium method. As these facts must be well known to the assembly of physicians and physiologists before whom the subject is now presented, the above mentioned introductory part of the article has been omitted.

gen. This cannot be done by a mere change-over, since at the juncture where air and hydrogen combine, the mixture becomes an explosive. But if the air is removed by replacement of a mixture of 4% oxygen and 96% nitrogen, the risk for explosion is completely eliminated.

It is of paramount importance that sufficient quantities of gas are available aboard a vessel when deep-sea diving is done with the aid of synthetic gas mixtures. To use hydrogen manufactured ashore and brought to the vessels in cylinders is not practicable, because of the great quantities used and the difficulty of transferring cylinders of gas from lighter to salvage vessels in heavy seas. In order to manufacture hydrogen aboard a vessel where there is little space, the ammonia-cracking process is preferable. Ammonia, NH_3, can easily be broken up into its component parts with the use of a catalyst—giving 75% hydrogen and 25% nitrogen. The only foreign element in the gas is 0.1% of ammonia, which can be removed with a gas filter. The nitrogen content is larger than desirable, for the breathing resistance is increased, but the partial pressure is never high enough to give a narcotic effect to the diver. By adding 4% oxygen to

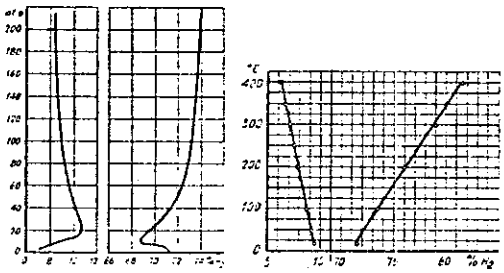

FIG. 3. Explosion limits for hydrogen-air as a function, to the left of the pressure, and to the right of the temperature.

the mixture, the final composition of the gas will be 72% H_2, 24% N_2, and 4% O_2. The mixing of the gas is done during compression (Fig. 4); a feed-pump coupled to the compressor adds oxygen to the low pressure side in desired quantities. The intermediate gas, used before changing to the hydrogen gas mixture, is made by burning cracked gas with an air surplus, the water vapor being condensed and the gas compressed in chambers.

DEVELOPMENT OF THE HYDROGEN METHOD

In order to develop the new hydrogen method, work has been carried on in two

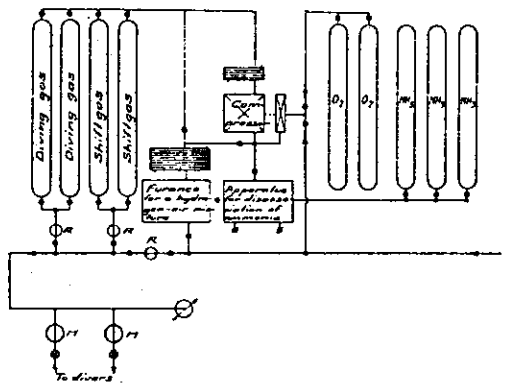

FIG. 4. Schema of a projected synthetical gas supply plant.

fields, the purely physiological and the practical application of the method.

Physiological research has been done by Dr. Yngve Zotterman, who began his studies during the summer of 1943 at the Caroline Institute in Stockholm. He began his research by studying the behavior of animals in various gases and at various pressures. The computation of decompression time intervals is a difficult problem since ternary gas mixtures were different with different partial pressures, varying physical solubility and diffusion speeds. Dr. Zotterman has shown with the use of graphs the varying saturation points in different types of cell tissues. Experiments with animals have been done at pressures representing a depth of 150 meters, and the animal most generally used was a cat (Fig. 5). It was shown that the animal did not show any afteraffects from the experiments with gas mixtures, but that great care had to be used in the decompression process.

The work on the construction and building of special auxiliary apparatus has been

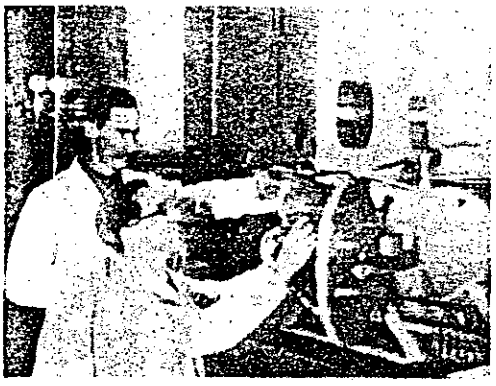

FIG. 5. High pressure chamber at the Caroline Institute; the test animal did just successfully slip out.

done under the auspices of naval engineer Anders Lindén of the Naval Supply Corps. Diving attempts have been made by myself at sea to test different gases and to determine how a diver reacted to them. The attempt from *Belos* to a depth of 40 meters was very successful (Fig. 6 and 7). The voice of the diver, because of the high speed of sound in hydrogen, becomes nasal and indistinct, which might necessitate using Morse code from greater depths. The diver is also apt to feel the low temperature of the water sooner because of the higher heat conductivity of hydrogen gas, wherefore pre-heating of the gas is desirable.

I made another diving attempt to a depth

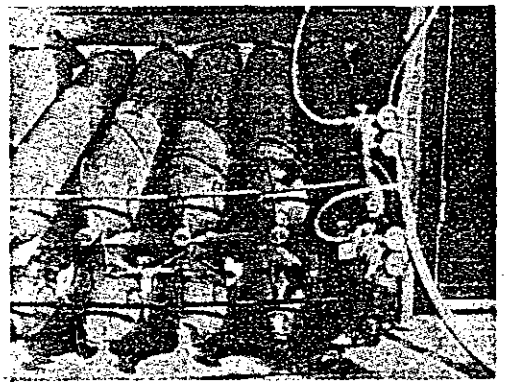

FIG. 6. Gas batteries with "shifgas" and "diving gas" at the first trial on board "Belos."

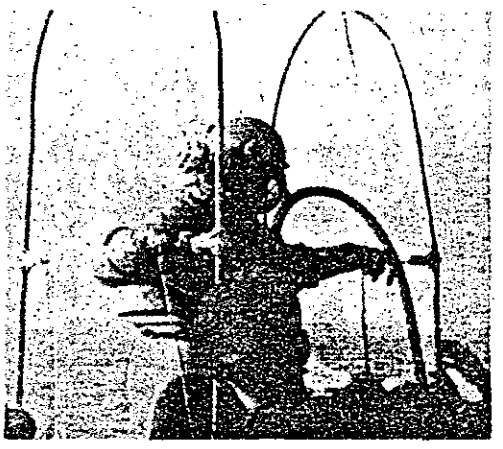

FIG. 7. The descent starts.

of 110 meters on 14 December 1944, which showed that the breathing resistance was small and the narcotic effect nil, thus making it possible for divers to carry on work at this depth. The attempt showed that the maximum depth had not been reached. The trials will be conducted up to a depth of 150 meters. The possibilities of coming to the assistance of a crew aboard a sunken submarine are therefore greatly enhanced with this new method, for which the naval authorities have shown a great interest and the greatest cooperation.

HYPERBARIC OXYGEN THERAPY

Articles selected by Jefferson C. Davis, M.D.
Colonel, MC, USAF

11

HYPERBARIC OXYGEN THERAPY

J. C. DAVIS

Results of experiments on mice to elucidate the mechanism of carbonic oxide (carbon monoxide) poisoning in coal mines were first reported by Haldane in 1895. He determined the protection afforded by high inspired oxygen tensions at 3 ATA, even with very high CO percentages. At 3 ATA, 5.2 volumes percent of oxygen were physically dissolved in blood, nearly the normal oxygen consumption of the body. This observation paved the way for Boeremas' "Life Without Blood" experiments as well as hyperbaric oxygen treatment of CO poisoning. Haldane further made the important observation that physically dissolved oxygen is more readily available to tissues than hemoglobin-bound oxygen, and that this is independent of shifts in the oxyhemoglobin dissociation curve.

Sixty years later, in 1955, Churchill-Davidson et al. presented the rationale, techniques, and preliminary results of the first clinical trials of irradiation tumors while patients breathed hyperbaric oxygen. This paper was responsible for further studies worldwide, although long-term results in follow-up have been largely disappointing.

The first report of surgery performed in a hyperbaric chamber to make use of plasma-dissolved oxygen to extend the safe time for circulatory arrest during heart surgery was made by Boerema et al. (1956).

In a powerful series of experiments, Boerema et al. (1960) demonstrated the potential for efficient oxygen delivery to tissues aside from, or in addition to, hemoglobin carriage. They reported studies on 27 pigs in which plasma or dextran was used to replace blood while the animals breathed oxygen at sea level or at 3 ATA. They found that pigs breathing air or oxygen at sea level could not tolerate a drop of hemoglobin percentage to below 10 percent (S). Hemoglobin levels of 0.6, 0.5, and 0.4 percent were tolerated for 45 minutes with no ECG changes from breathing oxygen at 3 ATA. Recovery occurred after reinfusion of blood.

Brummelkamp et al. (1961) presented the first controlled guinea pig studies which demonstrated the effectiveness of hyperbaric oxygen in the treatment of *Clostridium perfringens* wound infections. The paper reported on the first four patients with gas gangrene treated with hyperbaric oxygen. Controversy in the surgical community caused by this paper was finally settled 19 years later. Well over 1,000 cases of gas gangrene had been treated with hyperbaric oxygen around the world, with resultant reduction in mortality and tissue loss.

C. J. Lambertsen (1965) accurately assessed the state-of-the-art. After reviewing the physiology of oxygen toxicity, he focused attention on the direction research should take in the future. The paper is important because it marked a turning point in the quest for a proper role in medicine for hyperbaric oxygen.

In a paper on oxygen tension in healing tissue, I. A. Silver (1969) demonstrated that oxygen inhalation elevated the intercapillary oxygen gradient, which became the underpinning of later animal studies on oxygen dependency of wound healing. In his elegant studies at Cambridge, Dr. Silver used micro-electrodes to correlate distance from functioning capillaries, oxygen tension, fibroblast survival, fibroblastic division, and collagen formation.

Hunt et al. (1969) determined the oxygen tension pattern of healing wounds by using Teflon®-implanted coils in animal wounds. The hypothesis and data set forth in these studies laid the groundwork for successful clinical studies leading to current indications of hyperbaric oxygen in hypoxic wounds of soft tissue and bone.

Several years of conflicting studies focused on the possible use of hyperbaric oxygen to improve cognitive functioning in the elderly. Raskin et al. (1978) published a controlled study of 82 elderly patients with significant cognitive impairment. Hyperbaric oxygen, hyperbaric air, normobaric oxygen, and normobaric air were used. Immediate and follow-up studies failed to show any difference between the groups.

HYPERBARIC OXYGEN THERAPY

J. C. DAVIS

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Boerema I., Kroll J. A., Meyne N. G., Lokin E., Kroon B., Huiskes J. W.: High atmospheric pressure as an aid to cardiac surgery. *Arch Chir Neerl* 1956; 8:193–211. Copyright 1956, Academisch Ziekenhvis.

Boerema I., Meyne N. G., Brummelkamp W. K., Bouma S., Mensch M. H., Kamermans F., Stern Hanf N., Van Aalderen W.: Life without blood. A study of the influence of high atmospheric pressure and hypothermia on dilution of the blood. *J. Cardiovasc Surg* 1960; 1:133–146. Copyright 1960, Minerva Medica.

Brummelkamp W. H., Hogendijk J., Boerema I.: Treatment of anaerobic infections (Clostridial myositis) by drenching the tissues with oxygen under high atmospheric pressure. *Surgery* 1961; 49:299–302. (Abstract only)

Churchill-Davidson I., Sanger C., Thomlinson R. H.: High-pressure oxygen and radiotherapy. *Lancet* 1955; 1:1091–1095. Copyright 1955, Lancet.

Haldane J.: The relation of the action of carbonic oxide to oxygen tension. *J Physiol* 1895; 18:201–217.

Hunt T. K., Zederfeldt B., Goldstick T. K.: Oxygen and healing. *Am J Surg* 1969; 118:521–526. (Abstract only)

Lambertsen C. J.: Medical implications of high oxygen pressures. *Transactions & Studies of the College of Physicians of Philadelphia* 4 Ser. 1965; 33(1):1–18.

Raskin A., Gershon S., Crook T. H., Sathananthan G., Ferris S.: The effects of hyperbaric and normobaric oxygen on cognitive impairment in the elderly. *Arch Gen Psychiatry* 1978; 35:50–56. Copyright 1978, American Medical Assoc.

Silver I. A.: The measurement of oxygen tension in healing tissue. *Progr Resp Res* 1969; 3:124–135.

IN: Arch. chir. Neerl. 1956; 8:193–211.

From the University Surgical Clinic, Wilhelmina Gasthuis, Amsterdam

HIGH ATMOSPHERIC PRESSURE AS AN AID TO CARDIAC SURGERY *

by

PROF. DR. I. BOEREMA, J. A. KROLL AND N. G. MEYNE
Department of Surgery

E. LOKIN, B. KROON AND J. W. HUISKES
Department of Anaesthetics

I. *Introduction and review* (PROF. DR. I. BOEREMA)

At the present time surgeons everywhere are frantically searching for a better and safer method for operating upon the heart under direct vision. Long before a new idea or method has been elaborated in the laboratory, it has often already been tested clinically. This clinical application itself may often be considered as experimental surgery. Whatever one may think of this from a moral point of view, one may conclude from it that the necessity for finding a solution to the problem of intracardiac surgery is extremely urgent.

In view of the application of these new and sometimes premature ideas to clinical practice, it is impossible to give a survey of the present state of affairs based exclusively on animal experiments. Frequently, in order to form a conclusion, utilization of experience gained from such clinical work is necessary.

From a purely technical point of view, open intracardiac surgery offers no difficulties; splitting of valves, excision of tumours and closure of defects can be carried out in the same way as has been done for many years in various parts of the body. The only problem is how to approach the lesion.

If industry is taken as an example, the ideal would be stopping the motor during repairs. However, unlike the situation in industry, stopping the heart causes damage to all organs, including the heart itself. In other words the difficulty of the whole problem lies in the impossibility of stopping the circulation for any great length of time.

Following a temporary circulatory arrest, the central nervous system and cardiac musculature together form the Achilles heel amongst the organs of the body. In comparison consideration of other organs can be neglected.

The problem of reducing damage occurring as a result of temporary circulatory arrest has been approached in two ways.

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* Read before the *Société européenne de Chirurgie cardio-vasculaire* at Zurich, July 29th, 1956.

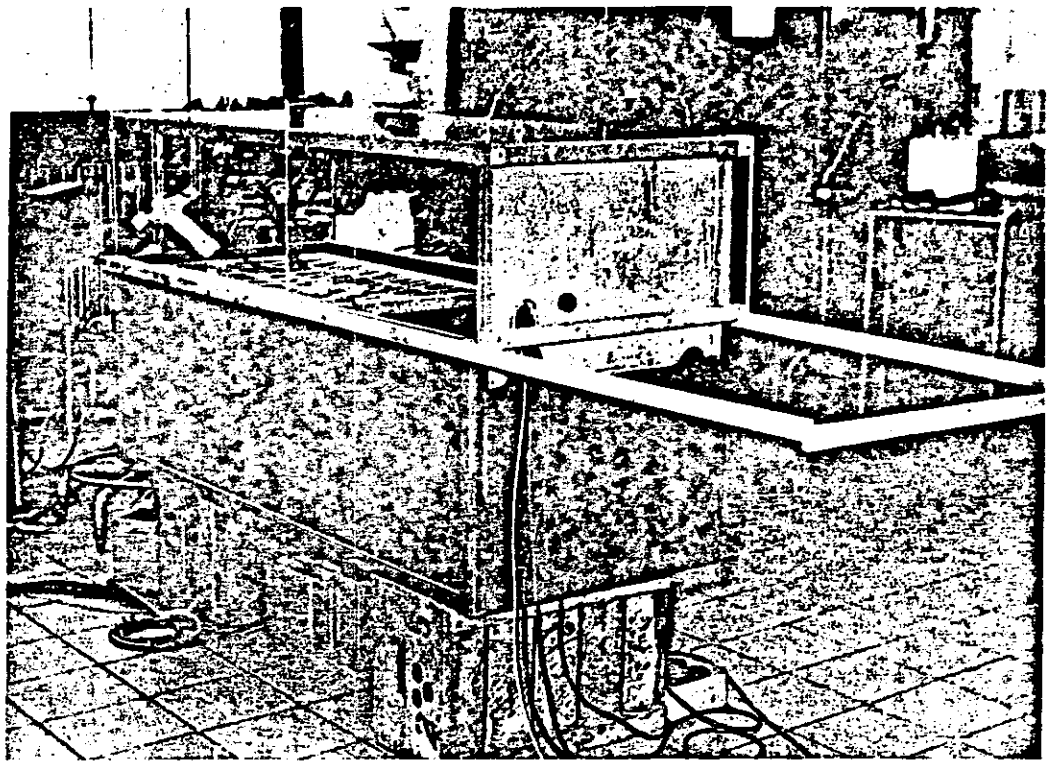

Fig. 1. The wooden chest with the transparent, deep, plastic lid (closed).

One way entails by-passing the heart, while the circulation is maintained. Only an ideal by-pass system will enable operations to be performed in the heart during a longer period of time. From a technical point of view it does not make much difference whether the heart is in a state of arrest or fibrillation or whether it keeps on beating. Ultimately, of course, following the repair, the heart must be capable of recovering its function.

There are many difficulties associated with the by-pass method; first, the operative preparation of the by-pass itself is no mean task; large vessels have to be opened and closed afterwards; the chance of making technical errors is great.

Secondly, utilization of the patient's own lung for oxygenation and elimination of carbon dioxide is but seldom possible. Consequently, oxygenators outside the body are necessary. Whether an isolated living lung preparation or a lung from a living donor or a machine is utilized for this purpose, the chances of technical difficulties arising and thus of deficiencies occurring during use, which immediately endanger the life of the patient, are great.

Regardless of the fact that by-pass methods have been succesfully used even clinically, in our opinion, a good, simple and safe method has not yet been found. The search for an ideal by-pass method continues, but discussion of this important problem is beyond the scope of this paper.

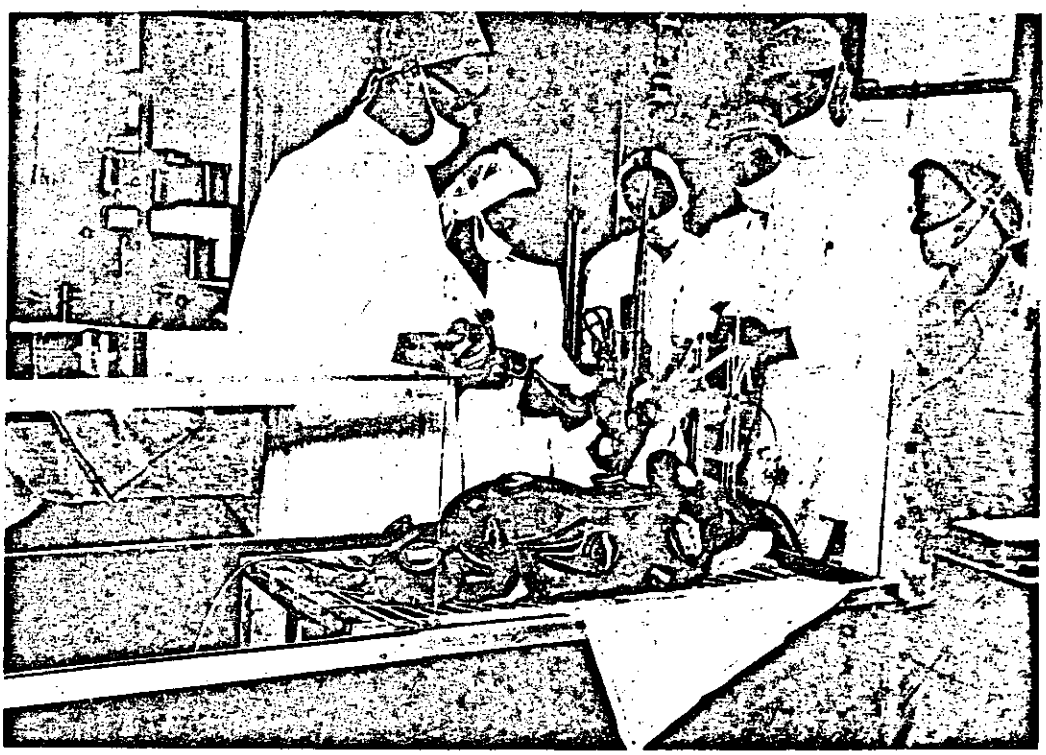

Fig. 2. Cooling of the patient to 28° C. (oesophagus).

The second and more acceptable method of reducing tissue damage lies in diminishing the need for a good circulation; in other words, to reduce the metabolic processes in the body. Under such circumstances the circulation can be arrested for some time. The term 'artificial hibernation' is applied when metabolism is reduced by chemical means, and 'hypothermia' when physical methods are used.

While reviewing hypothermia, it may be pointed out that when, in September 1948, experimental cooling of dogs was begun in this clinic with the object of finding a method for intracardiac surgery, the line of thought was thus:

With a fall in temperature all manifestations of life and functions of organs would diminish in intensity, perhaps not according to the RGT rule, but nevertheless resembling it. The length of time for which temporary circulatory arrest might be maintained without causing damage, and hence during which the heart could be opened, could be increased.

It was the idea of a slow motion picture with all actions and functions equally slowed down. The error of this concept, however, very soon became obvious and in our first publication in 1950,* attention was drawn to the fact that the principal

* Read before the Provincial Surgical Club of Great Britain, May 1950 and the Royal Dutch College of Surgeons December 1950. See: *Arch. Chir. Neerl.*, 1951, 3 (25) and *Nederl. Tijdschr. v. Geneesk.* 1951, 95 (2996).

reason for objecting to hypothermia was that this deviation rather limited the scope which hypothermia offered and still offers to surgery of the heart.

The functions of the various organs do not diminish gradually, parallel with the decreasing temperature. When the body temperature begins to fall, the metabolic rate does not fall, but, on the contrary, actually rises appreciably at first, through the resistance mechanism of the body. It is only after this resistance is eliminated or exhausted that metabolic processes are reduced evenly with the fall in temperature. So the living organism behaves quite differently from a dead body; it reacts against the insult by means of its biological powers of resistance.

Brain function also declines with fall in temperature but not parallel with the temperature. McMURREY, who studied brain function during hypothermia demonstrated (by means of the electro-encephalogram) that, down to 30° C., brain function was reduced only very little, that between 30° C. and 25° C. it was reduced appreciably and that below 25° C. only very little further reduction occurred.

The heart rate is reduced gradually. The conduction time in the heart appears to increase, but this does not occur gradually; below 26° C. it increases fairly rapidly, just as sensitivity to mechanical stimulation increases, with the result that at temperatures below 26° C. there is a dangerous tendency to ventricular fibrillation. The suprarenal gland secretions are diminished at low temperatures; the hypophysis does not produce ACTH below 27° C.

Thus, instead of a steady, even decline in function of the important body organs, rapid and slow decreases, and even increases, occur. Even in one particular organ this irregular decline can be shown. DURRER, working in this institute, demonstrated that the inner layers of the heart muscle were more readily damaged by hypothermia than the outer layers when blood cooling was used.

A complete dissociation of the normal co-operation between organs occurs, while, in our opinion, this co-operation is necessary for maintenance of physiological life. As a result of this dissociation, there is also a disturbance of enzyme reactions in the cells themselves.

Even more puzzling is the change in chemical blood values, the constancy of which is essential at normal temperatures. The blood sugar increases, acidity increases, potassium, calcium and sodium values change, water moves out of the cells into the extracellular spaces, internal secretions diminish. It is quite unknown whether these changes must be considered as a direct result of cooling, in which case they should be rectified, or whether they must be considered as a manifestation of resistance to danger on the part of the body, in which case they should be fortified. There is a tendency to clumping of the blood, its viscosity increases; in many blood vessels the circulation stops altogether, perhaps in an effort to maintain effective circulation in more important organs. Knowledge concerning changes in diffusion rates through membranes at various temperatures is completely lacking. However, these changes will be important, particularly when the temperatures at which lipoid coagulates, are approached. In man this temperature is approximately 17° C.

It is clear thus that, for example, at 30° C., 25° C., 20° C. etc. 'physiological'

Fig. 3. Patient at 28° C. (oesophageal) lying above the open, wooden chest, in which the air temperature is controllable in order to stabilize the temperature of the patient.

conditions exist, which differ completely from the known, familiar physiology at normal temperature. One book could be written about the 'physiology' of the body at 30° and another for the 'physiology' at 25° etc. These books would be quite different from each other. Up to the present, from information collected from all parts of the world, there is, as yet, no such survey available. In the author's opinion, until a good appreciation of the 'physiology' at low temperatures is possible, operations carried out at very low temperatures are comparable to gastric operations performed without adequate knowledge of anaesthesia, arrest of haemorrhage or asepsis. During the lecture on hypothermia in 1950, given by the author, mention was made of these shortcomings of hypothermia as an aid to surgery. The hope was expressed that these would be only temporary.

Further knowledge concerning cooling, collected from all over the world, which has been published since the original article from this clinic in 1950 and since BIGELOW's publication of his work, which was carried out independently in the same year, confirms the opinion expressed in that article.

It is not one deviation alone, for instance the change in the pH of blood, which brings danger in its wake, but rather the loss of a harmony and the dissociation of normal life processes, which cause death to occur, either during hypothermia, or

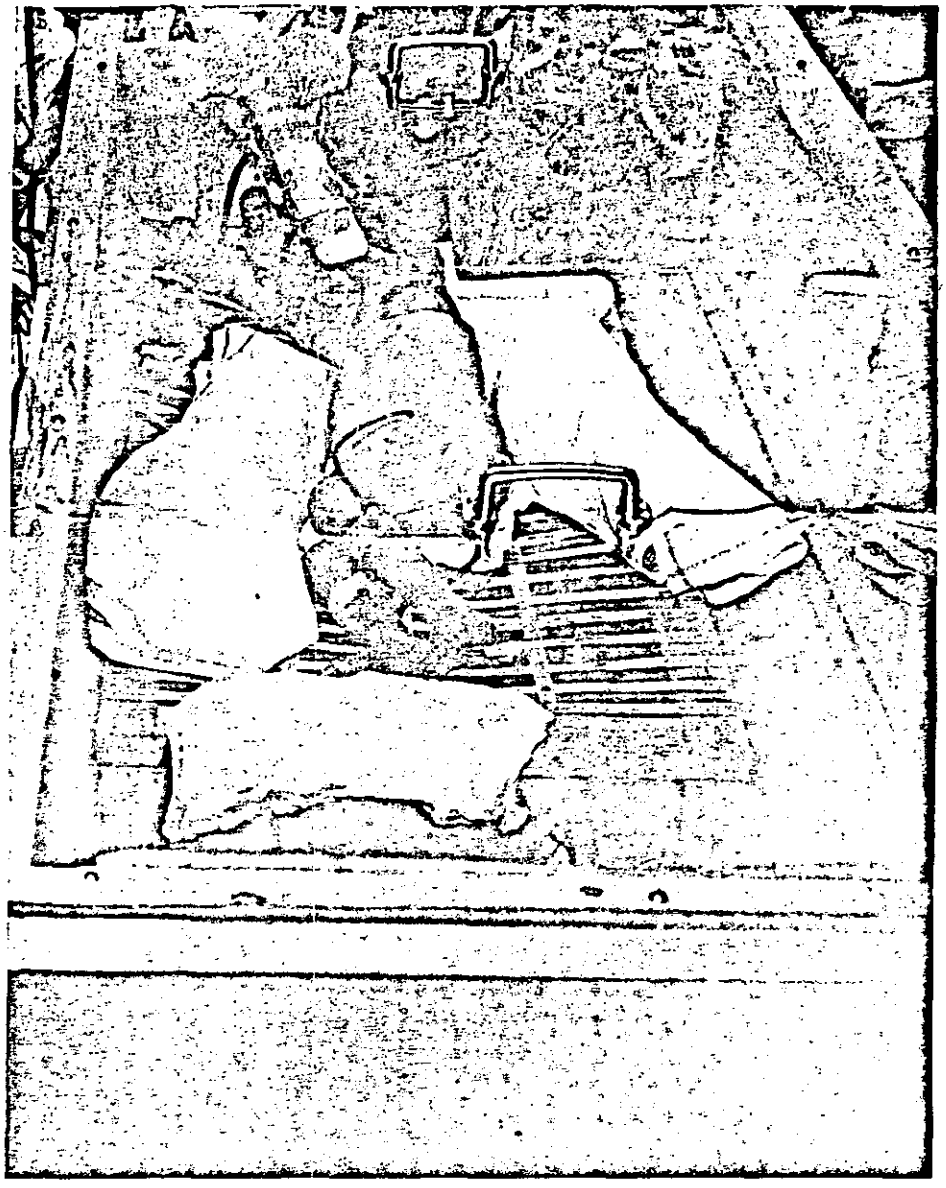

Fig. 4. Rewarming the patient with open thorax under the transparent, plastic lid of the wooden chest.

soon after the warming-up process. Both deaths should be considered as a direct result of hypothermia itself, in the former instance due, perhaps, to ventricular fibrillation and in the latter to shock.

Nevertheless from collected experience a few hopeful points now seem to be emerging. First, it seems that at temperatures below approximately 26° C. the dangers associated with hypothermia increase enormously. This dangerous border-

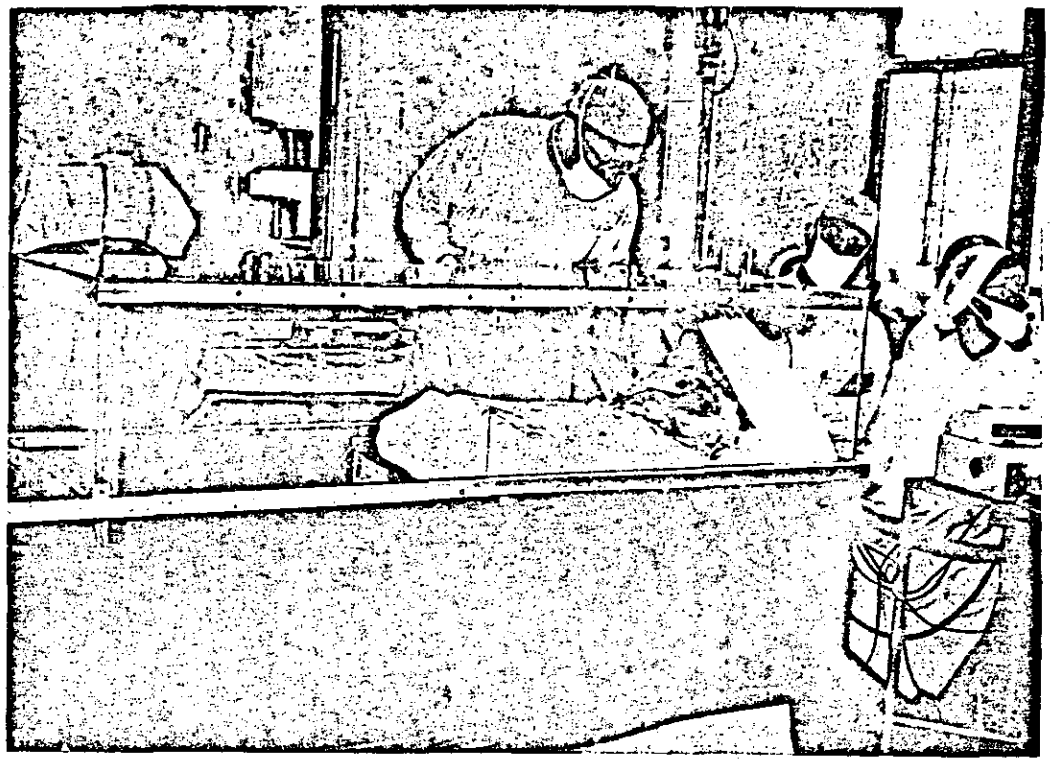

Fig. 5. Inspection through the transparent lid for possible intrathoracic haemorrhage while warming up is in process.

line was mentioned in the original article from this clinic. Cooling below 27° C.–26° C. appears, at the present time, undesirable, at least clinically. That small and particularly young animals have survived experimental cooling to 0° C. offers hope for the future; nevertheless the chance of the human adult surviving this is too small for the risk to be undertaken.

Instead of striving to cool to still lower temperatures, the author has endeavoured to cool safely to 27° C. and then to broaden the range of possibilities, without incurring the dangers of lower temperature levels. The fall in temperature to 27° C. should be carried out quickly. For this purpose the method we used was arterio-venous blood cooling. Later DELORME advised the use of veno-venous cooling. Blood cooling has the advantage that the whole body is cooled fairly evenly, both internally and externally. Surface cooling does not so efficiently achieve this. GOLLAN observed temperature differences as great as 20° between oesophagus and rectum, which are especially dangerous during the warming-up process, because the heart, which is colder and working slowly, has to contend with the demands of the already warmer surface tissues, which require a better circulation.

The blood cooling method, however, entails the use of heparin; the post-operative haemorrhages which are described, many of which are fatal, are probably a result

of using heparin; although damage to the capillaries by cold should not be forgotten as a cause of haemorrhage. So surface cooling was the method adopted.

It is repeatedly stated in the literature that during the operation the patient continues to fall in temperature, reaching values of 24° C. or 22° C. In other words, the temperature may fall below the critical danger level.

After intensive animal experiments, the following method was evolved and has already been applied to several children, in order to prevent this 'after-cooling.'

The patient is placed upon a net stretched across a large open wooden chest (*Fig. 1*) which serves as operating table. Surface cooling to 28° C. (oesophagus) with icebags is carried out (*Fig. 2*). Into the wooden chest cold or hot air can be blown. This air cushion serves as thermostat and the after-cooling is then completely controllable (*Fig. 3*). Further, this method has the advantage that the warming-up process can be started as soon as the period of circulatory arrest is over. When the operation on the heart itself is completed, the thorax is not closed—it is kept wide open. A deep, transparent, plastic lid is then placed on the top of the wooden chest, with the patient uncovered lying inside it (*Fig. 4*).

The air temperature in the wooden chest is 45° C. In this way re-warming occurs on the surface and inside the thorax. Children under two years of age reach a temperature of 35° in approximately an hour.*

During this warming-up process the thorax remains open and the surgeon can observe, through the transparant plastic lid, whether there is any haemorrhage (*Fig. 5*). We have seen it occur a few times; the lid was then removed, the haemorrhage arrested, the lid replaced and the warming-up process allowed to proceed. Only when the temperature is normal again is the thorax closed after careful inspection. Thus the surgeons operate in two stages, with a period of about an hour between the stages. The thorax is nevertheless still open for a shorter time than for instance during an aortic resection for isthmus stenosis at normal temperature.

It is possible that this late closure of the thorax will avoid the danger of post-operative haemorrhage, especially when heparin has been used. In this way even the arterio-venous cooling, which has fallen out of use, may once more prove to be valuable. At present, however, it seems probable that the external cooling and then rewarming with air is a safer method than extra-corporeal cooling of the blood.

The ultimate goal, *viz.* achievement of a complete cardiac arrest followed by a safe revival, is thus by no means achieved yet. Indeed, if the temperature is not reduced below 27° C., then metabolism is reduced by 50 per cent only; the pulse rate is reduced accordingly and the time available for circulatory arrest in the large blood vessels still is no longer than 6–8 minutes. In comparison, the maximum period of circulatory arrest possible without brain damage at normal temperature, is three-and-a-half minutes at most, so the gain is relatively great, but as an absolute value it is still short. According to GOLLAN even at 19° C. the circulation cannot be arrested

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* At the Second European Congress of Cardiology, September 1956 an apparatus, designed on the same lines, was shown by ADAMS RAY (not yet published).

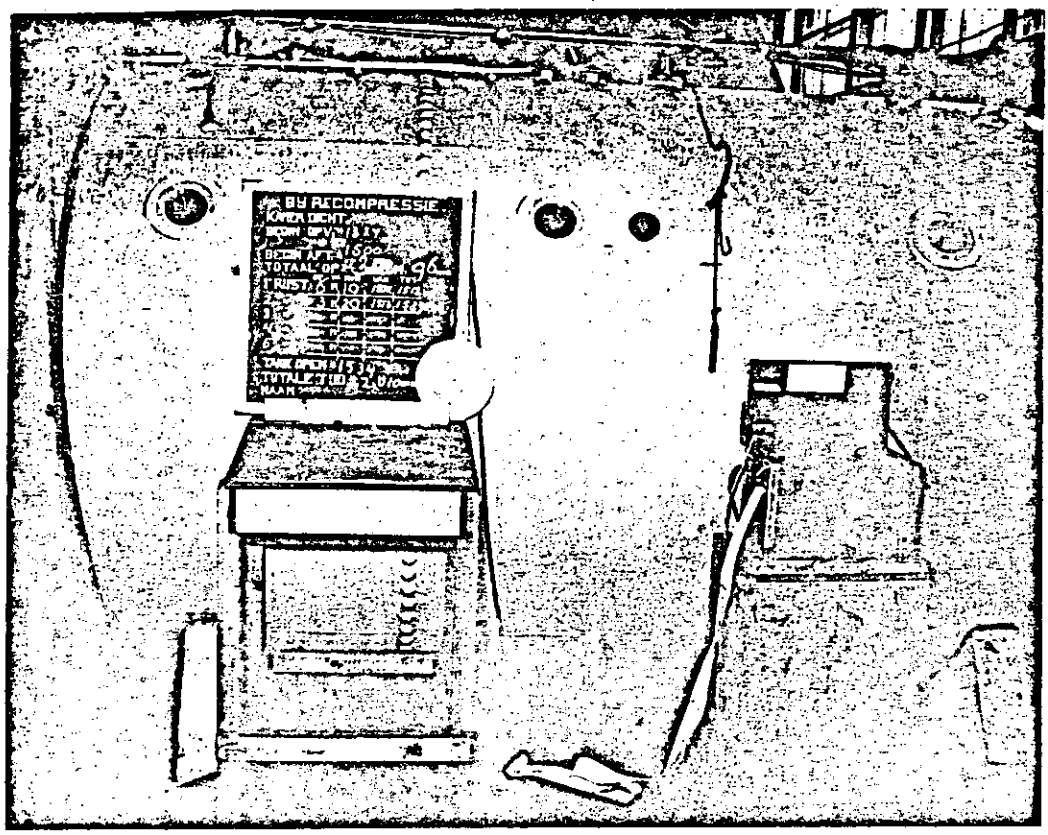

Fig. 6. The high pressure tank.

for more than 12 minutes. Major, complicated, intracardiac operations of long duration cannot be performed.

A method must, therefore, be sought which will enable the circulation to be arrested for a longer period of time, yet without the necessity of deep cooling.

II. *Atmospheric high pressure for surgical animal experiments* (PROF. DR. I. BOEREMA, J. A. KROLL, N. G. MEYNE, E. LOKIN, B. KROON AND J. W. HUISKES)

The drawback to the normal oxygen supply in the body is the absence of a reservoir where oxygen can be stored. An attempt has been made to overcome this disadvantage by saturating the whole body with oxygen during the cooling process. The tissues, which then function at a much slower pace, use up this reserve of oxygen at a very slow rate; only an intensively working organ would rapidly use up this reserve. The slowly functioning, cooled brain can, in this way, withstand a long period without additional oxygen, but the beating heart is less favourably affected.

In spite of the fact that at 27° C. the shift to the left of the oxygen dissociation curve of oxyhaemoglobin presents no danger, yet the amount of oxygen which

oxyhaemoglobin can release is limited. The tissues themselves contain very little dissolved oxygen.

If pure oxygen is inhaled, then the amount of oxygen dissolved physically is probably five times greater than when air is inhaled. At 27° C. the solubility of oxygen is a little more than at 37° C., nevertheless this amount is actually small. The amount of oxygen in physical solution increases greatly when the atmospheric pressure is raised. If oxygen is inhaled at three atmospheres absolute pressure, then the amount of oxygen in physical solution is probably fifteen times as much as is found in blood normally. This oxygen is completely available and independent of the dissociation curve. Remembering that at 27° C., the oxygen requirements of the body are reduced by 50 per cent, the conclusion is formed that an individual at 27° C. breathing pure oxygen at a pressure of three atmospheres absolute, in all probability does not require haemoglobin. The utilized oxygen is replaced again by physical solution in the blood as the lungs are traversed. Moreover, this great increase in the amount of oxygen in solution is found not only in the blood, but also in the extracellular fluids and probably even in the cells themselves. The tissues have thus a large store of oxygen available when the circulation is arrested. It seems possible that this fact would be of great importance by induced fibrillation as carried out by SHUMWAY & LEWIS, SENNING & KAPLAN, GLENN & SEWELL, LAM *et al.*, BJÖRK.

The affect of increased atmospheric pressure on animals has been a subject of investigation and experiment for more than a century. Its influence on all organs, especially the heart, has been studied in full detail. LUTZ, using pressure as high as seven atmospheres absolute, made electrocardiographic investigations.

However, to the authors' knowledge, operative procedures have never been carried out inside a high pressure caisson, in order to increase the possibilities of surgical procedures. Placing animals in a high pressure tank and observing them through the wall of the tank or, as CHURCHILL–DAVIDSON described recently, irradiating a patient with cancer in a small caisson under a pressure of a few atmospheres is of less value for progress in surgery. It is imperative that the surgeons themselves enter the high pressure tank and carry out experimental operations on animals, just as in a normal operating theatre.

The increase in pressure should be such that working in it for a few hours is possible without danger to the operators themselves. Oxygen intoxication occurs only when pure oxygen at more than three atmospheres absolute pressure is inhaled for more than three hours. Intoxication causes convulsions, damage to the lungs, collapse and psychological disorders. When air is inhaled at a pressure of three atmospheres absolute, there is no danger of nitrogen narcosis, although some members of this team noticed a slight impairment of intellectual functions. At a pressure of three atmospheres absolute, it is quite possible to work safely (*Figs. 6* and *7*). The precautionary measures undertaken will not be discussed here.

The authors have now worked many times in a caisson in which the pressure was raised to three atmospheres absolute. Room air was breathed. The anaesthetized animals, all intubed, were ventilated with pure oxygen while the pressure was

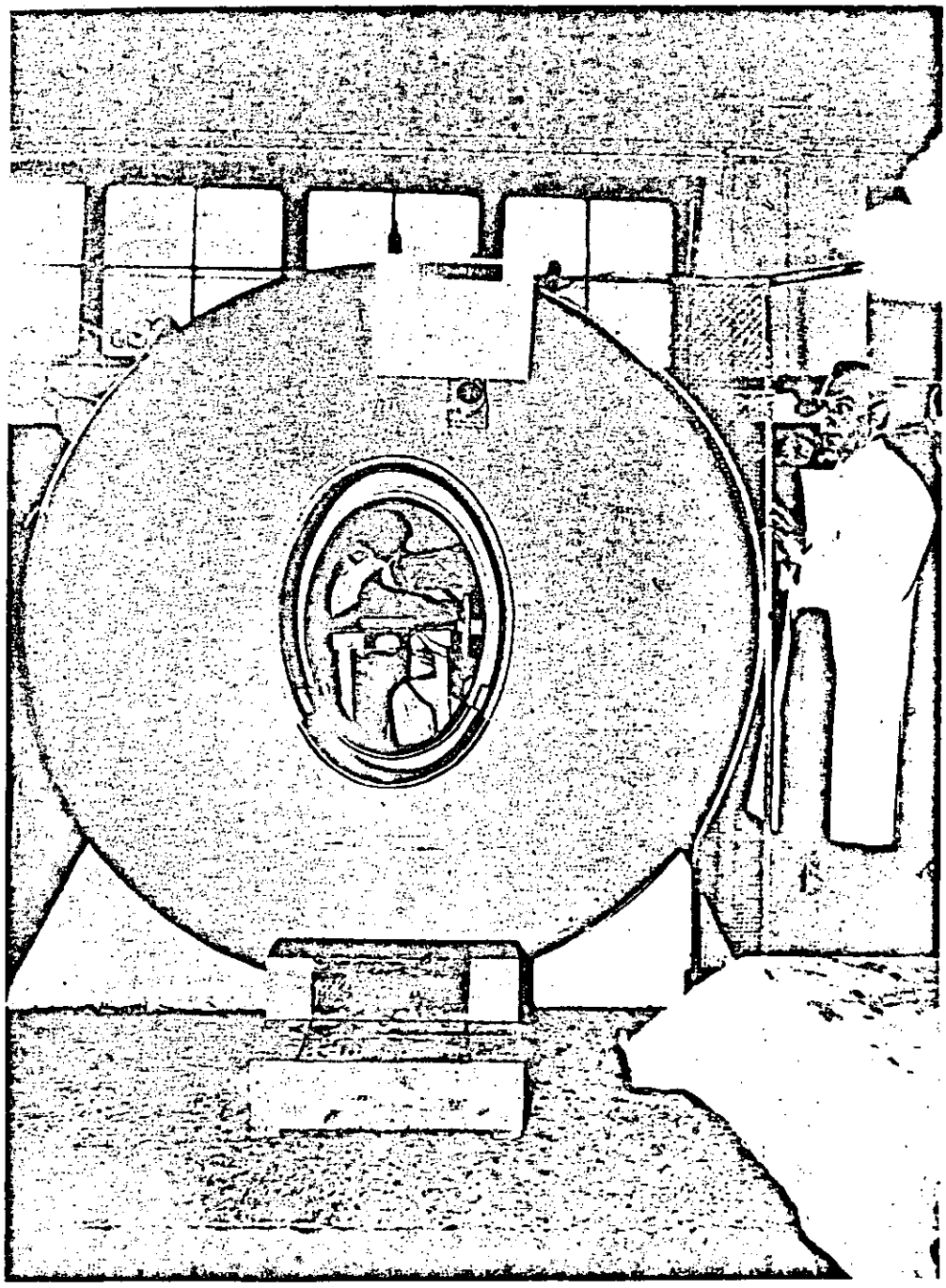

Fig. 7. The high pressure tank just before closure of the doors.

being raised and consequently they were saturated with oxygen. The intrathoracic operations were performed under the same conditions as in a normal operating theatre (*Figs. 8* and *9*).

Although the oxygen in physical solution throughout the body is wholly available, this does not prove that the cells can utilize it; cooling has deleterious influences on the intracellular enzyme processes, in the sense of a slowing down of the processes and a disturbance of the harmony existing between the various enzymes. Oxygen intoxication resulting from an excess of oxygen or from a lack of oxygen as a result of too low a pressure produces the same disturbances in the oxidation processes in the tissues (BEAN). Only experiment can prove whether saturation of the tissues with oxygen will allow stagnation of the circulation for a longer period of time.

For the optimal concentration and pressure of oxygen required, further investigations must still be carried out. For the experiments described in this article pure oxygen at a pressure of three atmospheres absolute was used and no damage to cerebrum or heart was observed; neither was there an increase in excitability of the myocardium—rather the contrary was observed.

The significance of this saturation with oxygen for surgical purposes is not so easy to prove. However, on incising the skin the bright red colour of the blood is striking; apparently there is far less reduction of oxyhaemoglobin than occurs normally. On opening the right ventricle of the heart under high pressure it is also evident that the blood coming out of the coronary sinus is less dark than usual. Apparently the physically dissolved oxygen supplied, for the most part, the oxygen requirements of the heart muscle; the oxyhaemoglobin was less necessary. Further, cyanosis of the tongue, which becomes apparent after both venae cavae were clamped, appears much later in the high pressure tank than at normal atmospheric pressure.

The inflow of blood to the heart can be stopped by ligating both venae cavae and with the aid of the electrocardiogram grave anoxia of the heart muscle can be demonstrated. At 27° C. with oxygen ventilation and at normal atmospheric pressure after clamping both venae cavae for 30 minutes, there are no signs of grave anoxia visible on the electrocardiogram. In the animals (rabbits) which were used for these experiments, minor changes in the electrocardiogram (depression of the ST segment, negative T waves) appear, at normal atmospheric pressure and ventilation with oxygen, after 5½–8½ minutes; at three atmospheres oxygen pressure these changes appear only after 12–13 minutes; sometimes after 45 minutes there are still no signs of them.

There is no proof, however, that these deviations in the electrocardiogram are due to anoxia; should they be due to anoxia, then the beneficial effect of high pressure in these experiments is evident. Reference to this will be made later.

There are three methods for proving whether saturation with oxygen under high pressure is beneficial to the central nervous system.

First, by studying the electro-encephalogram. It was impossible to use this method in our experiments.

Secondly, by recording signs of irritation of the brain. During the ventilation

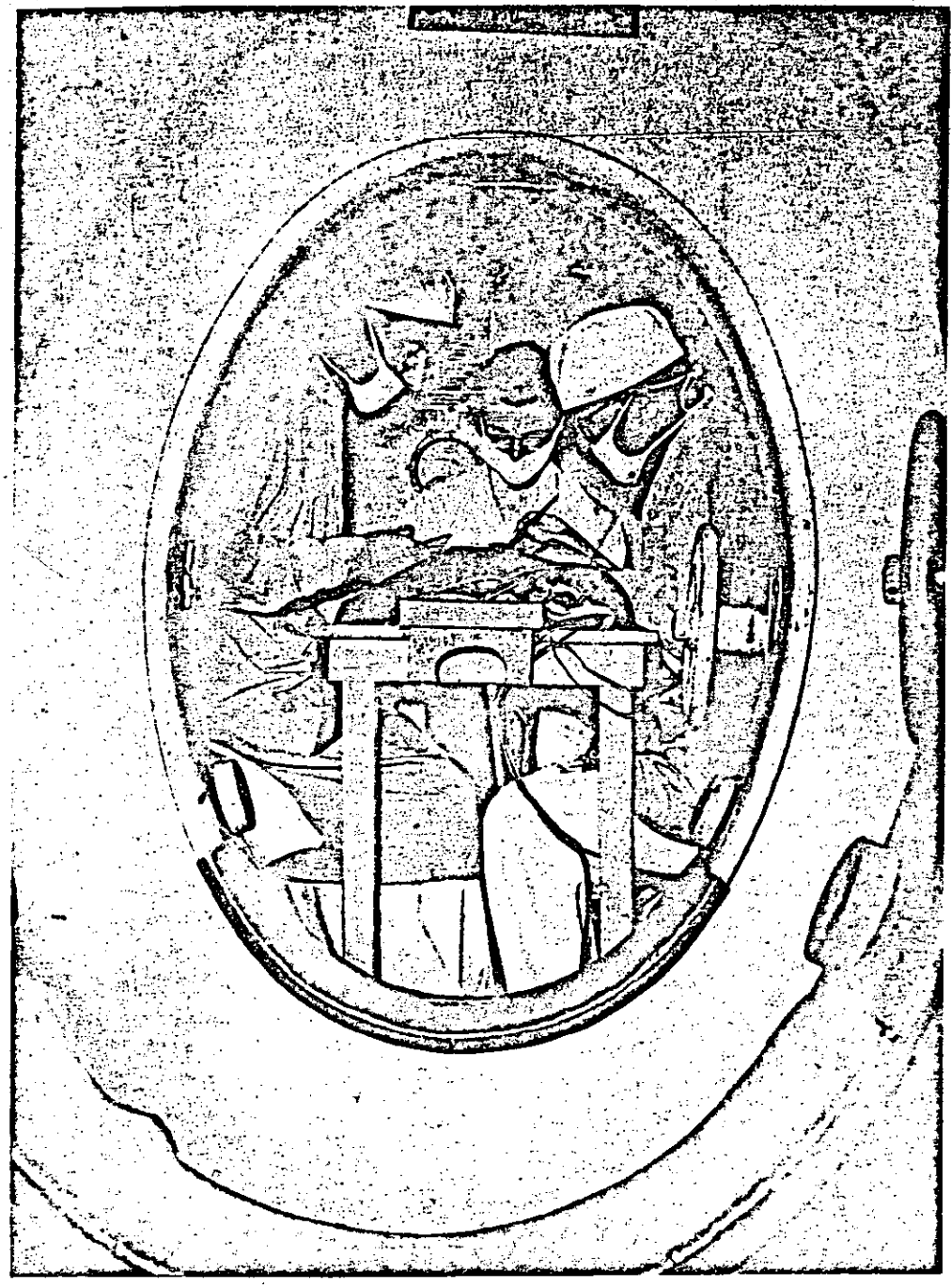

Fig. 8. Surgeons and anaesthetist ready for work in the tank. Doors have to be closed, after which the inside pressure is brought up to 3 atmospheres absolute.

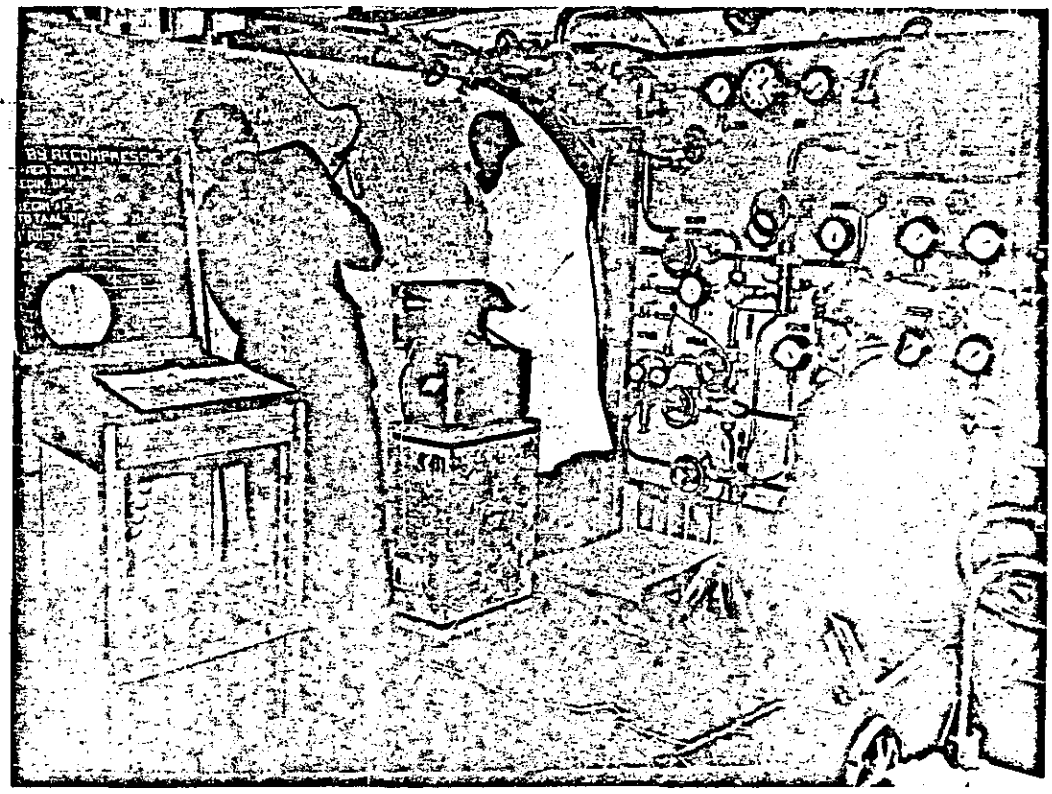

Fig. 9. Operation is performed inside the high pressure tank. Electrocardiographic observations of the heart of the animal is done outside the tank.

with oxygen at normal atmospheric pressure and at a body temperature of 27° C., under nembutal anaesthesia and succinylcholine paralysis, violent cramps in both upper and lower extremities were often observed approximately 8 minutes after clamping both venae cavae. Under similar conditions, but using an oxygen pressure of three atmospheres absolute for ventilation in the caisson, these cramps, which make the recording of a legible electrocardiogram impossible, were rarely observed and then only after 14 minutes. The animals in both series were cooled to 27°–28° C; whereby metabolism and accumulation of carbon dioxide in the brains during stagnation of circulation would be the same; the difference, therefore, must be due to the store of oxygen in the brain of the animal, which is living under increased atmospheric pressure.

Thirdly, total recovery of the animal to normal following clamping of the circulation and rewarming can be investigated. Only recently attempts have been made in these experiments to determine these limits. Up to the present time, after clamping both venae cavae, *i.e.*, totally stopping the circulation in the brain, even for 45 minutes complete recovery occurred in the animals operated upon under increased atmospheric pressure. Probably therefore, this is not yet the upper limit for circu-

latory arrest. How much higher this limit lies above that for animals breathing oxygen at normal atmospheric pressure is still unknown.

The significance of clamping both venae cavae needs further analysis. It certainly does not cause a total arrest of the circulation through the heart. After clamping both venae cavae the blood circulates as follows: Lung → left heart → aorta → coronary arteries → coronary sinus → right heart → pulmonary artery → lung, etc. As long as some pressure exists in the aorta, some circulation will remain. (*Fig. 10*). Further, the possibility of a prolonged, although diminished circulation exists through the bronchial artery → lung → left heart → aorta → bronchial artery, in spite of clamping both venae cavae.

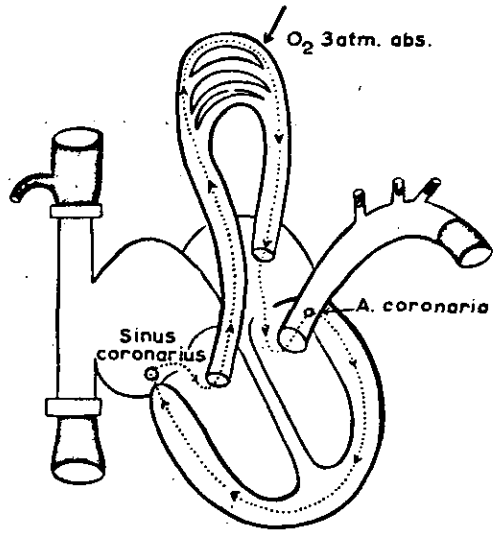

Fig. 10. Several minutes after clamping off the venae cavae some circulation through the coronary arteries is still present. Artificial respiration might be an important factor in this circulation.

In the rabbit the right atrium collapses after ligating both venae cavae, but although diminished, pulsations of the pulmonary artery in the hilus of the lung can be observed. In the caisson, under a pressure of three atmospheres absolute the right ventricle was opened and even after 15 minutes some blood could still be observed coming out of the coronary sinus into the heart. The heart muscle was able to take advantage of this circulation, in the first place for the elimination of products of metabolism, such as carbon dioxide, in the second place for the supply of oxygen, while the amount of physically dissolved oxygen in the blood, when the animal is ventilated with pure oxygen at a pressure of three atmospheres absolute is considerable. The solubility of oxygen in this blood still passing through the lungs has increased 15 times. All this oxygen can be utilized and the shift to the left of the oxygen dissociation curve offers no setback.

The question whether the heart actually suffers from lack of oxygen during a normal cooling, is still under discussion; possibly the study of the influence of increased pressure will provide the answer to this. The fact that defibrillation is more successful in a well oxygenated heart, points to the possibility that an oxygen deficit occurs during cooling; it also pleads in favour of maintenance of a coronary circulation during the cooling.

Knowledge gained in the field of cooling seems to point to the great importance of maintaining at least a certain circulation through the myocardium during the period of circulatory arrest. This is evident from the considerable difference in the time available for circulatory arrest, when only the inflow, or both the inflow and outflow, are blocked. In the latter case, the coronary circulation is almost

completely stopped, and damage of the heart muscle occurs much sooner.

The experiments of EDWARDS proved that infusion of oxygenated blood into the coronary system, during clamping of both inflow and outflow, prolonged the time available for intracardiac interventions considerably. The flow needs only be small. (ANDREASON & WATSON, LYNN, LILLEHEY, NAHAR, SCOTT).

Combining the experience of EDWARDS with our study of the use of high pressure, it may, in our opinion, be possible to provide an adequate circulation and oxygenation of the heart muscle, even if the total blood volume of an individual were to be replaced by a clear fluid, *e.g.*, plasma, provided ventilation with oxygen at three atmospheres absolute was applied. Should this be possible, then clamping of the in-and outflow of the heart or a by-pass or an oxygenator would no longer be necessary; the heart could be opened under a clear fluid and operated upon through it, while avoiding the dangers of anoxia and air-embolism. A series of experiments investigating this ideal is in progress. However, further statements would be premature.

That it is quite possible to carry out surgical procedures in a high pressure tank, which is equipped as an operating-theatre, is proven. Both surgeons and anaesthetists are able to work well under these conditions. The tissues, saturated with oxygen and inactive, are probably able to endure a long period of circulatory arrest, which, under other circumstances, would entail a danger far too great for the individual.

We live in a time in which biochemistry takes a dominant place in the study of the physiological processes of life—probably with justice. In 1950 one of us (I.B) and independently BIGELOW introduced a new principle, hypothermia as an aid to surgery, particularly heart-surgery, in which physical laws play a dominant rôle. Operating under conditions of increased pressure also introduces a new physical principle into surgery, which though needing further exploration, will, in the opinion of the authors again prove an aid to expanding the possibilities of heart surgery.

Summary

A critical review is given of cooling. A method is described for cooling and then warming up with air so that deep cooling is avoided and closure of the thorax is delayed until a normal temperature is reached.

The authors broadened the possibilities of moderate cooling (to 27° C.), described in the original publication of 1950, by operating in a high-pressure tank at three atmospheres absolute. Such a technique will possibly open a new field for research in surgery, especially surgery of the heart.

We wish to express our thanks to Captain B. POORTMAN for permission to carry out these experiments in the high pressure tank of the Royal Dutch Navy at Den Helder and to Lt. J. P. H. HUYSKENS, Lt. H. VAN HOEVEN and Lt. H. ITALIE, M.D., for their enthusiastic co-operation.

This work was carried out with financial aid from TNO (the Institute for Applied Physical Research).

Résumé

Les auteurs donnent un aperçu critique de refroidissement. Ils décrivent une méthode de refroidissement et de réchauffement prévenant une baisse trop prononçée de la température et qui en surplus permet de retarder la fermeture de la cage thoracique ouverte jusqu'au moment, où une température normale est atteinte.

Les auteurs augmentent les possibilités d'une hypothermie modérée (jusqu'à 27° C.) qu'ils ont décrite déjà dans une première communication en 1950 en opérant dans un caisson, qui contient une pression de trois atmosphères absolues. Cette technique peut probablement ouvrir un nouveau champ de recherche, surtout pour la chirurgie du coeur.

Zusammenfassung

Kritische Uebersicht über künstliche Kühlung. Beschreibung einer Kühl- und Aufwärmungsmethode, welche eine tiefe Nachkühlung verhindert und ausserdem die Möglichkeit schafft, das Schliessen des Thorax auszustellen, bis die normale Temperatur erreicht ist.

Die Verfasser verbreitern die Möglichkeiten der mässigen Kühlung (bis 27 °C.) welche von Ihnen bereits in der ursprünglichen Veröffentlichung im Jahre 1950 beschrieben worden ist, dadurch, dass sie in einem Caisson, mit einem absoluten Druck von 3 Atmosphären, operierten. Diese Technik kann eventuell ein neues Feld öffnen für Untersuchungen, welche es möglich machen, das Gebiet der Chirurgie, und besonders der Herzchirurgie zu erweitern.

Samenvatting

Een kritisch overzicht wordt gegeven over koeling. Een koel- en opwarmingsmethode wordt besproken, welke een te diepe nakoeling voorkomt en die bovendien de mogelijkheid schept om het sluiten van de open thorax uit te stellen totdat weer de normale temperatuur is bereikt.

De schrijvers verbreedden de mogelijkheden van matige koeling (tot 27° C.), door hen reeds beschreven in de oorspronkelijke publicatie van 1950, door te opereren in een caisson, waarin een druk heerst van 3 atmosfeer absoluut. Deze techniek zal mogelijk een nieuw veld openen voor onderzoek op het gebied van de chirurgie, speciaal de hartchirurgie.

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J. Cardiovasc. Surg. 1:133-146, 1960.

ORIGINAL PAPERS

Life without blood

(A study of the influence of high atmospheric pressure and hypothermia on dilution of the blood)

by

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S. BOUMA, M. H. MENSCH, F. KAMERMANS, M. STERN HANF
and W. VAN AALDEREN
(from the Surgical Department of the University of Amsterdam)

When in 1948 we (first al research) started our experiment on hypothermia[11 13] our ultimate aim was to reduce the metabolism of a warm-blooded animal to such an extent that all the physiological processes would almost come to a standstill.

If successful, this would enable the heart to be clamped off for a period long enough to allow for a major intracardiac operation to take place. When, however, we presented our results to the Netherlands Society of Surgeons in 1950 this aim had not been achieved by any means. In a hypothermic animal at about 27° C., the circulation could be stopped with good chances of survival for about twice as long as in a normothermic animal. The gain in time, about 100 per cent, was relatively great, but absolutely it was very modest, amounting to about five minutes; the reason for this was that below 26° C the physiology was altered too much and the normal harmony of life processes disturbed too much to allow for continuation of life or normal recovery by warming up.

Efforts to achieve safe conditions at a lower level of hypothermia so as to gain a greater period of time for clamping off the heart failed until recently, at any rate for animals with the same weight as human patients. So in 1956 we presented a series of experiments which showed that it was possible to clamp off the circulation for a greater length of time without lowering the temperature further than 27° C.[11 13] We operated on the animal in a pressure chamber at an absolute pressure of three atmospheres. The animal breathed pure oxygen, the investigators naturally breathed air.

Through the combination of inhaling pure oxygen and being under three atmospheres of pressure, the whole body was supersaturated with oxygen in physical solution.

(*) Professor of Surgery.

Again we are much indebted to T.N.O. (Institute for Applied Physical Research) for financial aid, to the staff of the Mijnendienst of the Royal Dutch Navy at Den Helder and to our adviser on technical matters, P. Bosma.

In blood plasma the oxygen is kept in simple physical solution, in equilibrium with the O_2 tension in the alveolar air. So by altering the O_2 tension in the lung alveoli the solubility in the plasma is directly influenced. Even a small lowering of this tension is known to be followed by alterations in respiration and circulation. [5 17]

The partial O_2 tension in the alveoli can be increased to about five times its normal value by breathing pure O_2 instead of air. When in addition the pressure of the inhaled O_2 is raised to three atmospheres the solubility of the O_2 in the plasma increases three times again. Thus the physical solution of O_2 in plasma, which when breathing air under normal atmospheric conditions comes to 0.3 volumes per cent, may increase to $0.3 \times 5 \times 3 = 4.5$ volumes per cent when breathing O_2 under a pressure of three atmospheres.

According to Campbell [14 15] the solubility of O_2 in fluids increases by 2.3 volumes per cent for every increase of one atmosphere. So according to this calculation the O_2 in physical solution may rise to 6.9 volumes per cent at a pressure of three atmospheres of pure oxygen. Naturally these calculations do not apply completely in practice. For instance the gas in the alveoli is never pure O_2 as it is mixed with expiratory gases from the blood, and moreover it is not certain whether this abnormal condition does not affect the simple diffusion via the alveolar membranes between the gas in the alveoli and the blood in the capillaries. Lambertsen, who measured the quantity of O_2 in physical solution in the blood after breathing O_2 at a pressure of 3.5 atmospheres, found this to be 6.5 volumes per cent. [23 26] That this percentage was even higher than that which we had first calculated was of course unpredictable. It was an unexpected advantage in our aims which are described below.

This increase of O_2 in physical solution is not confined to the blood plasma but it may be expected that the whole body, including the interstitial fluid and even the cells, may have the same increase of dissolved O_2. So the body is capable of storing more O_2 when O_2 is breathed at a pressure of three atmospheres. As this rise in the level of physically dissolved O_2 is not followed, at rest, by an increase in O_2 consumption, [14 15 20 21] this large reserve of O_2 in the body enabled us to stop the circulation for many more minutes than at normal pressure. This will be especially so when the need of oxygen of the body is decreased by hypothermia. This may be of great importance in surgery on the open heart. This supposition was confirmed by our experiments published in 1956.

In 1879 Fontaine had the same idea of increasing the solubility of gases in the blood by raising the atmospheric pressure of the inhaled gases. He raised the pressure by only 1/5 to 1/4 of an atmosphere in order to increase the quantity of N_2O dissolved in the blood by which means he intended to improve N_2O anaesthesia. He intended to build a high pressure operating theatre but did not succeed in doing so. As far as we know the idea of raising the percentage O_2 in solution was never suggested as an aid in operative surgery. An operating theatre for operations in a high pressure chamber has now been built in Amsterdam.

Besides the problem of increasing the amount of stored O_2 in solution in a high pressure chamber, another problem con-

cerning the transport of O_2 has arisen. Normally the O_2 is transported practically exclusively by means of oxyhaemoglobin.

In the tissue capillaries O_2 spreads from the plasma into the tissues and to the cells, the loss of O_2 dissolved in the plasma being made up immediately by the O_2 given off by oxyhaemoglobin. The oxyhaemoglobin, however, is not completely reduced, the extent of reduction being dependent on the activity and consequently the need of oxygen of the tissues.

At rest in the body as a whole the oxyhaemoglobin of 19 vols. per cent in the arteries is reduced to 14 vols. per cent in the capillaries. The need of the tissue at rest is thus seen to be 5 vols. per cent. Probably the physically dissolved O_2 is almost entirely available for the tissues. So, if a level of 5 vols. per cent of O_2 in physical solution in the plasma could be reached, the necessary transport of O_2 from the lungs to the tissues could be provided by the plasma alone; reduction of oxyhaemoglobin or even haemoglobin itself would no longer be necessary. Others investigators have halso come to this conclusion.[2 4 10]

However, different organs need different quantities of O_2. The brain is particularly vulnerable in this respect. According to Lambertsen the arteriovenous difference in oxygen content in the brain is 6.1 vols. per cent or slightly below the quantity of O_2 in physical solution at 3.5 atmospheres, but slightly above our calculated figure at three atmospheres which comes to a content of about 4.5 vols. per cent in plasma. So it appears doubtful whether breathing O_2 at three atmospheres will provide enough transport of O_2 to the tissues by means of physical solution only. Furthermore it is not clear that the normal physiological behaviour of the body will not upset our expectations. It is well known that breathing O_2 at increased pressure for a certain length of time will be followed by dangerous symptoms which are usually considered to be signs of oxygen intoxication. Enzymatic processes in all cells of the body are affected. The brain and the lungs especially are in danger, psychical changes and lung oedema developing in animals as well as in man during the experiments. However, if the O_2 pressure is not raised too much and the time of exposure not extended for too long the dangers may be avoided. In our opinion the great disagreements in the literature may be ascribed to the great differences in the pressures which are used. The effects of pressures of up to 5, or 8 and even more atmospheres are examined experimentally. The conclusions from these experiments are most confusing probably because the results at one level of pressure are often applied and accepted to be true also for lower levels of pressure. So we used only pressures which are expected to be useful in surgery without being harmful to the subject or the operating team in the pressure chamber. Furthermore it is no use leaving the animal in a state of abundance of O_2 for a longer period of time than is necessary for a normal operation.

As Behnke came to the conclusion that breathing O_2 at three atmospheres can be continued without harm for three hours, we decided to use a pressure of three atmospheres in our pressure chamber to be used for operations, and never to keep the animal, and in due course the patient, at this pressure for more than three hours. So it seems that the increase of the O_2 tension in the blood is better tolerated than a decrease (see von Euler *et al.*).

Nevertheless there is an important alteration in the physiology in particular

of the brain under these conditions because the inhalation of O_2 under increased pressure is followed by an increased resistance in the vascular bed in the brain and consequently by a decrease in cerebral blood circulation. Lambertsen concluded that the resistance rose to 55 per cent at a pressure of 3.5 atmospheres of O_2 and the flow decreased by 25 per cent; Kety and Schmidt [22 23] found an increase of vascular resistance of 35 per cent.

Thus we considered it quite impossible to predict what would happen to the animal in the tank breathing O_2 at an absolute pressure of three atmospheres. We decided, after an extensive study of the most confusing literature, to find, by experiments, the answer to the question: is the plasma able to take over completely the O_2 transport role of the haemoglobin under the conditions described above?

On paper the answer might be expected to be negative, judging by our calculation. The quantity of O_2 transported might probably be just insufficient to answer the O_2 need of the tissues. We therefore thought that it would be necessary to use hypothermia as well in order to reduce O_2 need. Originally, in 1956, when we studied the problem from this angle, we wanted to widen the field of surgical possibilities created by hypothermia by adding high pressure.

In this article, however, we first studied the problem from the other angle: would the tissues accept the high level of O_2 in physical solution? Would the transport of CO_2 from the tissue to the lungs be disturbed in the absence of reduced haemoglobin?

1. The answer could be found by lowering the quantity of haemoglobin and finding the lowest level still compatible with normal or satisfactory physiology.

The most important point was survival of the animal. This implied a statistical elaboration of the experiments and consequently the sacrifice of a very large number of animals.

2. Psychical disturbances could be used to judge the lowest satisfactory haemoglobin level. The animal might either fail to recover from anaesthesia or show neurological and psychical disturbances after the experiment. This would also entail a very extensive statistical study.

3. During general anaesthesia the heart of the animal beats in a normal manner, maintaining normal circulation and blood pressure, and is therefore ideal for studying oxygen consumption during our experiments.

It is well known that normally the heart needs a lot of oxygen. The ECG allows us to see whether the amount of O_2 supplied to the heart muscle is sufficient for normal function and so it gives us a means of finding out at which moment the quantity of O_2 supplied fails to be enough for normal heart function. At high atmospheric pressure the value of ECG readings is unaltered; Curtiss Hoff [16] found that at 3.75 atmospheres the ECG did not show changes concerning conduction of impulses or potentials. The only deviation, and that a minimal one, which could be found he ascribed to the altered position of the heart as a result of the lowered position of the diaphragm. We were able to confirm these observations. Furthermore, from continuous blood pressure readings we can obtain important information regarding the efficiency of the circulation and the moment at which it starts to fail.

We therefore registered continuous pressure readings and electrocardiograms

while we were decreasing the quantity of haemoglobin in animals at various atmospheric pressures. When the critical level had been reached the haemoglobin content was again raised to a normal level. Besides this, the experiment was only considered successful when the animal woke up and showed postoperatively the same normal behaviour as previous to the experiment. As it is well known that signs of damage may occur long after treatment in a highpressure tank the animal ought to survive the experiments for several weeks if one is to speak of success.

We diluted the blood by extracting it via a tube in the femoral artery and infusing a clear fluid not containing haemoglobin into the femoral vein. The rate at which plasma was run in was regulated by measuring the rate of spontaneous outflow from the femoral artery so as to make the inflow rate at any moment almost exactly the same as the outflow rate.

In our first experiments we used plasma. Very large quantities of plasma are needed. As the blood of pigs is available in slaughterhouses in any quantity required we used piglets as experimental animals twenty-seven times. Heparin was added to this blood and plasma obtained by centrifugation.

We later abandoned the plasma and used macrodex. To saltless macrodex containing 6 per cent dextran, and 5 per cent glucose, salts were added to form a solution similar to that of Ringer's solution.

It proved to be very important at any given moment to replace exactly the amount of blood taken from the artery. The temperature of the infused fluid should be the same as that of the animal.

The animals were anaesthetized with nembutal and pethidine and breathed pure oxygen. Curare was given in very low quantities only when shivering disturbed the ECG readings. We found that spontaneous respiration stayed almost normal even when the haemoglobin was very low. The corneal reflexes remained present. The respiration was often too superficial, however, so that there was a tendency for the pH to fall. As the experiment developed, we therefore used artificial respiration by means of an intratracheal tube. The blood pressure was read by means of a mercury manometer connected with a plastic tube introduced into the other femoral artery.

In three pigs weighing about 12 Kg, the blood was washed out of the circulation as described above by means of plasma or macrodex under normal atmospheric conditions. In all cases the results were about the same. When the level of the haemoglobin fell to 10, 11 or 12 per cent Sahli, the ECG showed disturbances (S—T depression) which were interpreted as signs of severe anoxia of the heart muscle. At this moment the blood pressure usually dropped. The inflow and outflow were then stopped. This level was maintained for fifteen minutes. If the ECG abnormalities did not then indicate a recovery from the cardiac ischaemia, it was concluded that the lowest tolerable level of haemoglobin had been reached. Stored blood of other pigs was then infused until the preoperative haemoglobin level was reached. The ECG almost immediately showed normal oxygenation of the heart muscle. The animals left the operation table in good condition and showed no disturbances during the next feio weeks.

We may therefore conclude that a haemoglobin percentage (Sahli) of lower than 10 will not be tolerated by the working heart muscle at normal pressure. Even when breathing oxygen, the

physically dissolved oxygen does not exclude the need for haemoglobin.

The same experiment was repeated in a highpressure tank where the atmospheric pressure was increased three times. The animal, during artificial respiration by means of an intratracheal tube, was consequently oxygenated by oxygen at a pressure of three atmospheres. Now we found that the haemoglobin level could be decreased much lower than at normal pressure. When after several experiments all the difficulties were mastered, and we saw that the animals survived the experiments, we were finally able to wash out practically all of the red cells. In the last series all the animals survived. The lowest haemoglobin levels were 0.6, 0.5 and once even 0.4 per cent.

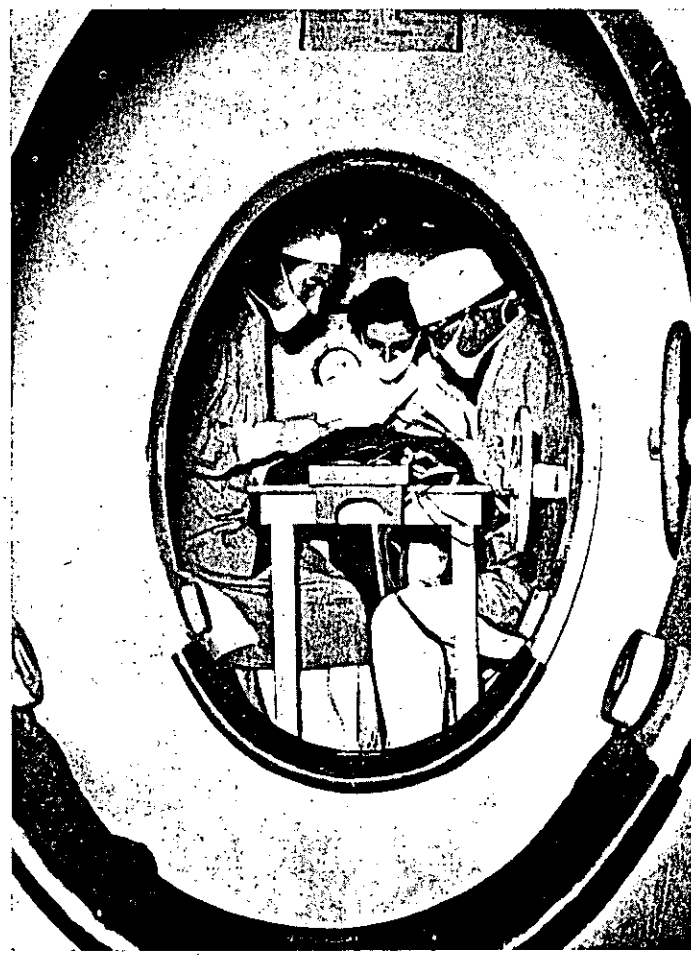

Fig. 1.—Operation in hyperpressure tank.

In the last cases macrodex was used instead of plasma. Even here the results were good.

At the lowest haemoglobin level in the experiment, *i.e.*, after replacement of

blood by seven bottles of macrodex, containing 575 ml. each, the animal was left at that low level for from five to fifteen minutes. During this time the haemoglobin level spontaneously rose slightly. The conclusion is that during this experiment in some organs there may be some pooling of erythrocytes, which are slowly brought back into the circulation. Wagner supposed sludge formation.

haemoglobin levels. A red foaming fluid streamed out of the mouth. This was sucked, off, until rales could no longer be heard in the lungs. Recovery was uneventful. We feel that this might be ascribed to insufficient spontaneous respiration. Since we systematically used artificial respiration during the whole experiment, lung oedema was seldom met. However, the speed of the re-infu-

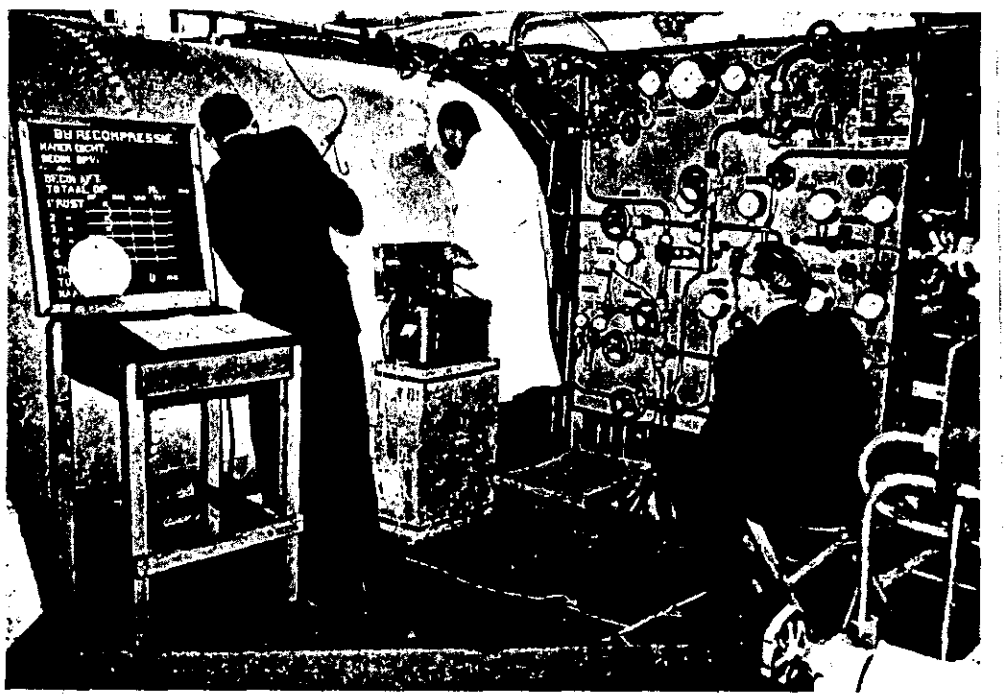

Fig. 2.—Electrocardiographic control outside the tank.

After this, heparinized blood of pigs was infused until the percentage of haemoglobin rose to the same level as before the experiment. After the operation the pressure was brought down to normal atmospheric pressure. Artificial respiration was continued until normal respiration returned.

In some cases we saw a rather severe oedema of the lungs developing at low

sion or the chemical composition of macrodex may also have influenced the development of pulmonary oedema. We do not believe that the transient pulmonary oedema in some of our cases was due to oxygen intoxication. As described in the literature (see Lambertsen), in our cases also the apnoea usually lasted for several hours. During this time artificial respiration was continued, first

with O_2, later with air. When finally spontaneous respiration set in, recovery came very quickly and soon the animals woke up.

might be caused by the fact that, being without any haemoglobin, the blood lost half of its buffering capacity. On the other hand it may also be possible that

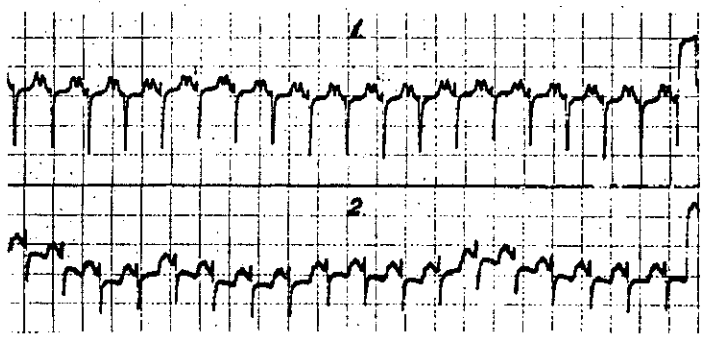

Fig. 3.—Pig 143. ECG showing anoxia at a haemoglobin level of 12.5 per cent at normal atmospheric pressure.

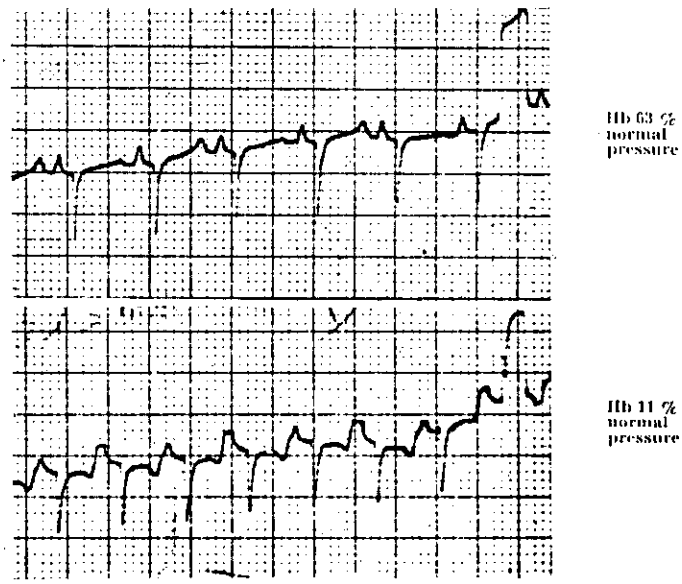

Fig. 4.—Pig 154. ECG showing anoxia at a haemoglobin level of 11 per cent at normal atmospheric pressure.

The figures show that the deep fall of the haemoglobin level was followed by a decrease of the pH. This could be influenced but was not prevented by hyperventilation. This decrease of the pH under these conditions there are pathological changes in the diffusion membrane between air and blood in the alveoli, which had not yet caused pulmonary oedema, but had already disturbed a

normal elimination of CO_2.[1] However, Fraenkl found that in dogs breathing in 2 or 3 atmospheres there was no increase in the CO_2 content of the blood. when the haemoglobin was 2.6 per cent, the pH had become 7.26, the bicarbonate content 15.7 meq. and the pCO_2 36 mm. Hg. Then there was a pause of fifteen

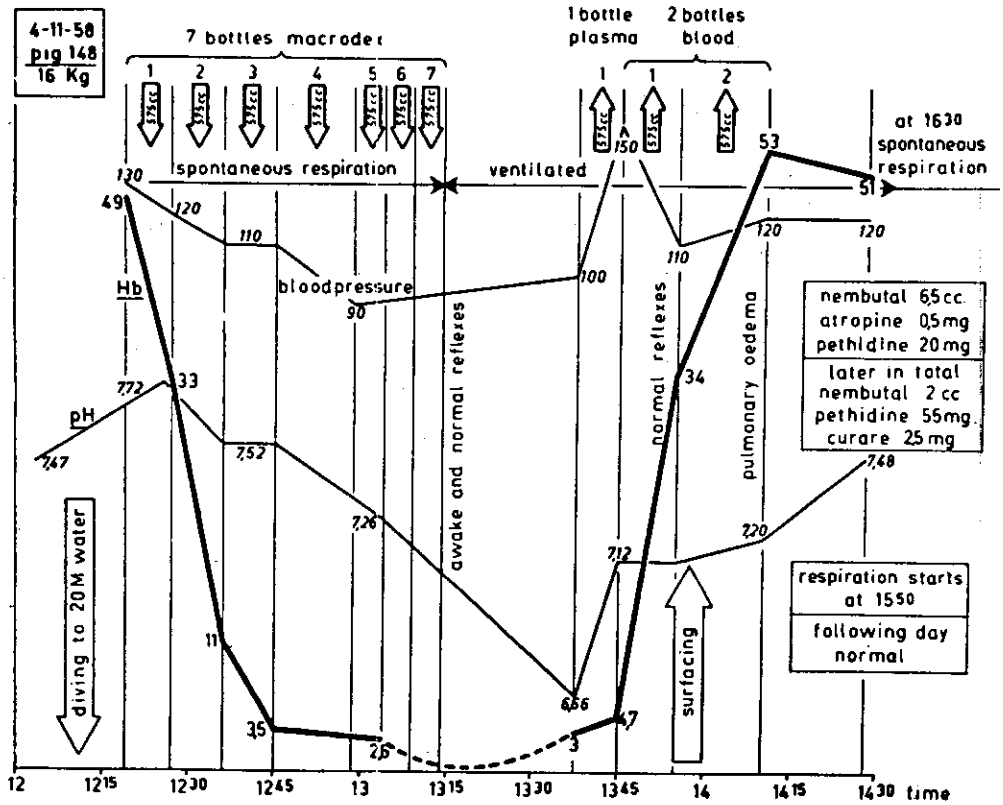

Fig. 5.—Dilution of the blood at a pressure of 3 atmospheres. The level of the haemoglobin went down to 2.6 per cent after infusion of 5 bottles of macrodex and probably still lower after infusion of two more bottles. At this level normal reflexes, some spontaneous respiration and the awakening of the animal. pH went down to 6.66 for a moment. Blood pressure never below 90 mm. Hg. Good recovery after infusion of one bottle of plasma and two bottles of blood. Next day normal. Died later on from pulmonary complications.

The registration of the alkali reserve showed:

Just before the dilution of the blood with macrodex, pig no. 148 had a pH of 7.72; the bicarbonate content was 26.2 meq. litre and the corresponding pCO_2 20 mm. Hg. During the dilution there was a steady decrease of pH. At the end, minutes, during which time the pig still showed signs of spontaneous respiration. This observation and the resistance of the animal to artificial respiration was the cause of an inadequate ventilation. The pH decreased to 6.66; the bicarbonate was 18.3 meq. and the pCO_2 over 80 mm. Hg. The pig, however, recovered

from this condition; the next day the animal walked and ate normally. This pig died later on from pulmonary complications.

In the same experiment with pig no. 152 the results showed a similar picture. The pH before dilution was 7.73, the bicarbonate content 19.7 meq. and the tilation, may be due to the elimination of haemoglobin, as the CO_2 could not be transported as a carbamine compound.

Our experiments therefore proved that under these conditions an animal can live for at least 45 minutes without any disturbances of the ECG, with a haemoglobin level lying beneath that at

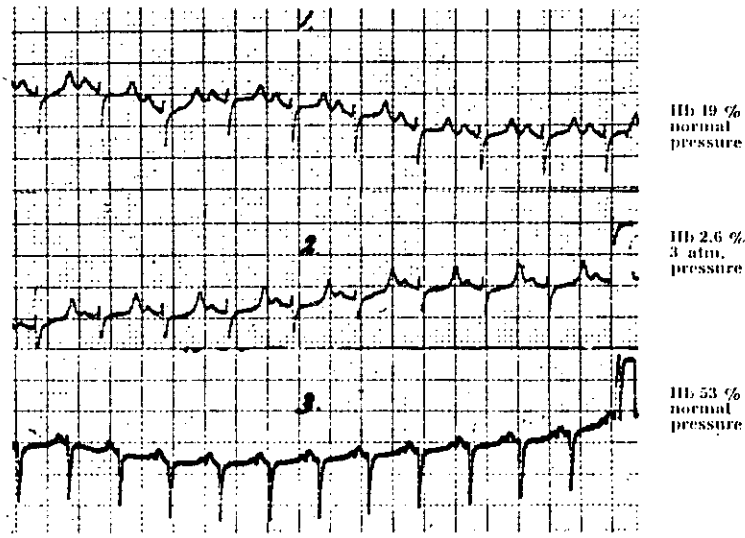

Fig. 6.—Pig 148 1. ECG before the experiment at normal atmospheric pressure: 2. ECG showing no signs of anoxia after dilution with macrodex to a haemoglobin level of 2.6 per cent at a pressure of 3 atmospheres; 3. ECG normal. Haemoglobin level back to 53 per cent at normal atmospheric pressure.

corresponding pCO_2 14 mm. Hg. So there was a respiratory alkalosis. At the end of dilution (haemoglobin 0.5 per cent) the pH was 7.07, bicarbonate content 11.9 meq. with a pCO_2 of 43 mm. Hg. Unfortunately we took no blood sample after the 5-minute period during which haemoglobin was at 0.5 per cent. After the blood transfusion the pH level recovered: seventeen minutes after the start of transfusion we measured a pH of 7.29, bicarbonate content 11.9 meq. and pCO_2 25 mm. The relatively high pCO_2 in the period of dilution, in spite of hyperven- which under normal atmospheric conditions severe signs of anoxia appear. Even with practically no haemoglobin in the vascular bed, using a biological fluid like plasma in the circulation, or a non-biological fluid like macrodex, there was enough trasport of O_2 to the heart wall to enable this organ to maintain its normal action, at least for fifteen minutes. This must be due to the transport of physically dissolved O_2.

We may therefore conclude that even without hypothermia the respiration of oxygen under a pressure of three atmos-

pheres, enables an animal to live with a haemoglobin level lower than 10 per cent (which is normally incompatible with life) for at least 45 minutes, and even to live without haemoglobin for at least 15 minutes.

circumstances which resemble the conditions thought by us necessary for our experiments. In these fishes the physically dissolved oxygen fulfils all requirements, but the fishes are rather slow in their movements. Perhaps other fishes

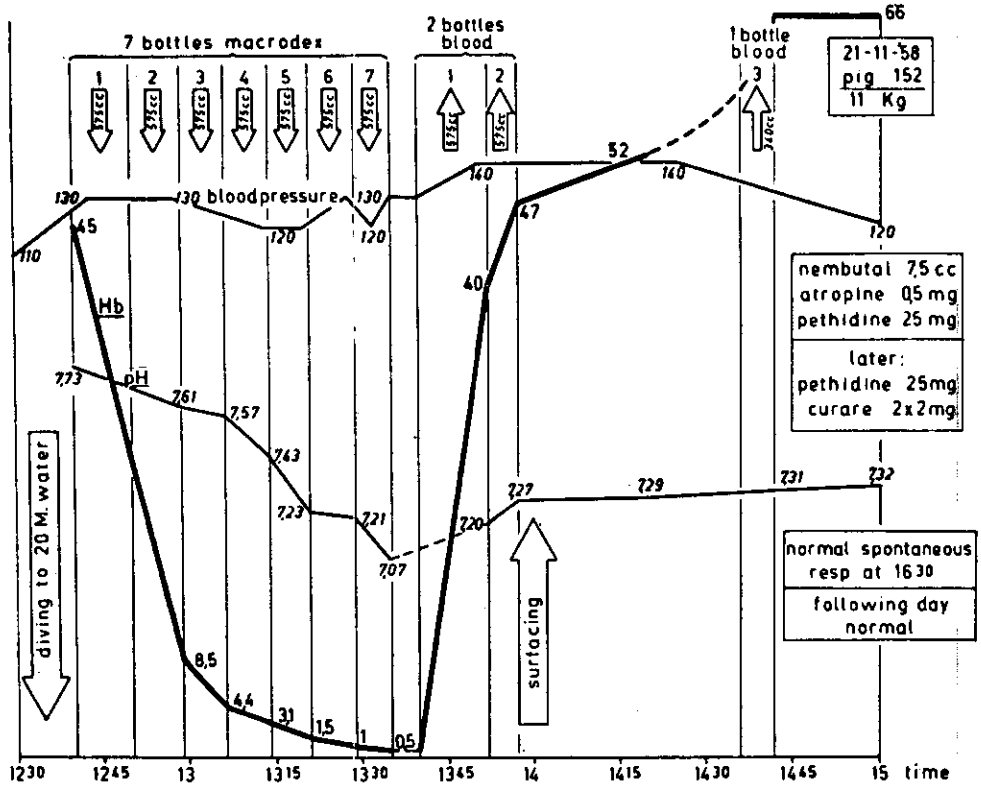

Fig. 7.—Pig 152. Dilution of the blood at a pressure of 3 atmospheres with 7 bottles of macrodex. The level of the haemoglobin at the lowest point was 0.5 per cent, pH went down to 7.07. Blood pressure practically unchanged during the whole experiment. Recovery to normal after infusion of two bottles of blood. Next day quite normal.

Among the vertebrates there is only one, very rare and only recently described family of fishes (*Chaenichthyidae*) which has no haemoglobin and no corpuscles apart from some leucocytes in its plasma.[30 37] These fishes live at the bottom of the fjords of South Georgia in very cold and well aerated seawater—

in the polar seas also require no haemoglobin when at rest or moving slowly. Haemoglobin is then a kind of luxury, only necessary during exertion (Munro Fox).

Except for these very rare species, there are no vertebrates without red blood cells. Having red blood cells is one of

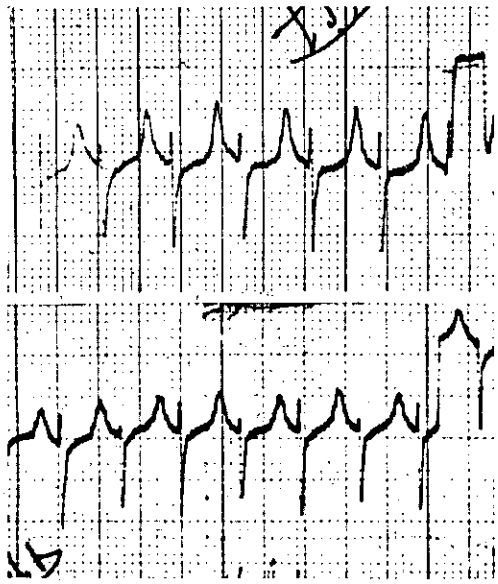

Fig. 8.—Pig. 152. 1. ECG before the experiment at normal atmospheric pressure; 2. ECG showing no signs of anoxia after dilution with macrodex to a haemoglobin level of 0.5 per cent at a pressure of three atmospheres.

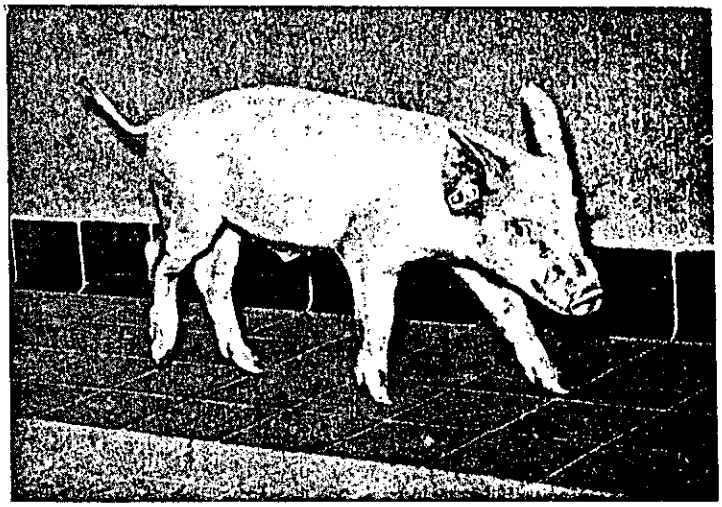

Fig. 9. -Pig 152. Normal behaviour the next day after dilution of blood to 0.5 % haemoglobin.

the characteristics of vertebrates. Our experiments prove, however, that this characteristic is not an absolute necessity. Under certain circumstances even warm-blood ed animals can live without red blood cells and even without a biological fluid in the vessels.

Nevertheless, in another series of experiments we tried to find out the importance of hypothermia in animals kept

in a highpressure tank. Twenty piglets of 12.5 to 16.5 Kg (average 13.7 Kg) were used.

Nine of them were cooled under normal pressure to 30° C; at this temperature the blood was diluted with macrodex in the same way as described above. ECG readings showed the limit of the dilution. Four of the piglets died for different reasons (haemorrhage, ventricular fibrillation in a case where the dilution had gone too far), five survived. It was shown in all five cases that at a haemoglobin level of 8 or 9 %, a change in the ECG reading developed in consequence of an anoxia of the heart muscle; just as, in the series described above, there was a lowering of the pH and the alkaline reserve and a rise of the pCO_2. For instance, pig. 161 at 30°:

Before the dilution		After dilution
pH	7.68	7.39
alkal. reserve	28.6 meq./L	23.8 meq./L
pCO_2	34.5 mm.Hg	41 mm.Hg

From this series we can conclude that hypothermia down to 30° C does not allow an important lowering of the haemoglobin content of the blood as compared to normothermic animals, the difference being about 3 % haemoglobin.

At the same temperature of 30° C eleven piglets were brought under a pressure of 3 atmospheres. The dilution of the blood was again performed with macrodex-glucose-salts.

Six of the animals died (two from ventricular fibrillation; one from hypotension caused by disturbance in the conduction system in the heart; three from technical difficulties).

The five survivors were all normal again after reinfusion of blood.

In all cases there developed changes in the ECG when about 4 % haemoglobin was reached; a complete restoration occurred after reinfusion of blood. The changes in pH, alkaline reserve and pCO_2 were like those in the former series of experiments. However, the changes in the ECG were not to be ascribed to anoxia, but seemed to be a consequence of irritability of the heart muscle. So it seems to us that the lowering of the fibrillation threshold of the heart muscle, caused by hypothermia, is already present at a haemoglobin percentage which does not cause any anoxia at all; as compared to the results of the experiments in normothermic animals, where haemoglobin levels of 0.4 % were reached without any sign of anoxia.

So our experiments have shown that the combination of high atmospheric pressure and hypothermia has no advantage over highpressure alone of normothermic piglets.

Summary.—The authors lowered the level of haemoglobin in young pigs to 0.4 per cent, exchanging the blood by plasma or by macrodex. The animals, breathing oxygen at a pressure of three atmospheres in a highpressure tank, lived for 45 minutes with a level of haemoglobin not compatible with life when at normal atmospheric pressure. They were kept alive, practically without any haemoglobin (0.4 per cent) for fifteen minutes. During all this time the ECG no showed pathological changes, the circulation and the blood pressure remained spontaneously normal. Recovery was uneventful after re-infusion of normal blood. The combination of highpressure and hypothermia proved to have no advantage over highpressure alone.

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TREATMENT OF ANAEROBIC INFECTIONS (CLOSTRIDIAL MYOSITIS) BY DRENCHING THE TISSUES WITH OXYGEN UNDER HIGH ATMOSPHERIC PRESSURE.

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SUMMARY

Drenching the tissues with oxygen by means of inhalation of pure oxygen in a hyperpressure tank under a pressure of 3 atmospheres (absolute) was introduced as an aid in the treatment of anaerobic infections. Four patients (Cullen ulcer and clostridial myositis) were treated successfully in this manner.

HIGH-PRESSURE OXYGEN AND RADIOTHERAPY

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A PRELIMINARY investigation has been made into the effects of irradiating carcinomata in patients breathing oxygen at a pressure of three atmospheres absolute (30 lb. per square inch gauge pressure). This was suggested by the findings of Gray et al. (1953), who showed that the sensitivity of tumour cells to irradiation was increased in mice breathing oxygen.

It appears to be a general principle that the sensitivity of all cells to irradiation is related to the oxygen concentration in their environment. This sensitivity increases rapidly as the oxygen concentration increases to a critical level above which there is little further change.

Evidence has been obtained from the structure of neoplasms that they contain cells which, in relation to those of normal tissues, are in a poor state of oxygenation (Thomlinson and Gray 1954, 1955). An increase in the concentration of oxygen around these cells would therefore cause a relatively greater increase in their sensitivity to irradiation.

This encouraged us to investigate the possibility of improving the treatment of patients. Firstly we considered the physiological and technical problems involved. To reach a pressure of three atmospheres a pressure chamber is required. Exposure to oxygen at high pressure for more than short periods is liable to cause convulsions (Bert 1878, Thomson 1935, Donald 1947, Lambertsen et al. 1953). In animals, however, the onset of convulsions can be retarded by barbiturate anæsthesia (Marks 1944, Taylor 1954, Churchill-Davidson 1954). We have therefore anæsthetised our patients before the administration of oxygen. They were thus not susceptible to alarm at being enclosed in the chamber or to the severe pain which is sometimes felt in the paranasal sinuses in atmospheres of high pressure.

Because of the possibility of extensive rupture of the tympanic membrane or hæmorrhage in the middle ear bilateral myringotomy was done. Small polyethylene tubes, such as have been used in the treatment of chronic secretory otitis media (Armstrong 1954), kept the perforations patent during treatment.

It is impossible to remain in the same room as the pressure chamber during irradiation, but contact with the patient can be maintained electrically. We have used an electrocardiograph, an electromyograph from the upper lip to detect the possible onset of convulsions, and a thermistor mounted on the outlet of a carbon-dioxide-absorbing canister to obtain a tracing of the respiratory rate. Special precautions were necessary to avoid static or other sparking because of the risk of fire or explosion.

We used a modified naval diving recompression chamber (fig. 1). This consists of a steel cylinder measuring internally 7 ft. 6 in. × 2 ft. 6 in. with a door at the head and secured by swing bolts. It is mounted on four swivel wheels and can be moved by two people although it weighs two tons. There are two observation ports in the door, and on top of the chamber is a recessed window 25 cm. sq. of 1 in. 'Perspex' through which the patient is irradiated. At the foot end of the chamber is an inlet manifold connected directly to four 120 cu. ft. oxygen

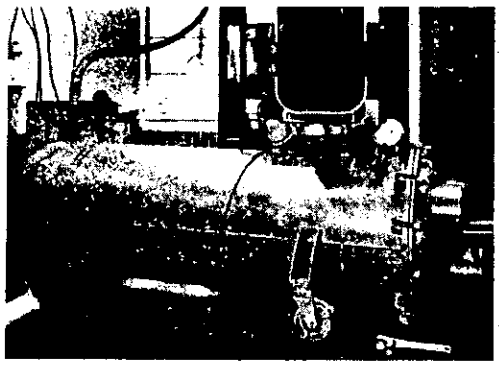

Fig. 1—Pressure chamber in position under X-ray unit.

cylinders without reducing valves. A pressure gauge is attached to the manifold. There are also a safety valve and a $1^1/_4$-in. exhaust valve from which the oxygen is discharged from the building through a hose-pipe. At the head end of the chamber are a gauge measuring the pressure within the chamber, a fine needle exhaust valve, and a second safety valve. Inside the chamber is staging on to which slides a metal trolley carrying the patient. To get this easily in and out of the chamber a second trolley has been made on to which the first slides (fig. 2). The electrical leads pass out of the chamber through a pressure gland and are connected via twin amplifiers to a double-beam cathode-ray tube. One beam is used to make the tracing from the thermistor and the other to make a combined tracing from the electrocardiograph and electromyograph. A second cathode-ray tube and camera enable these tracings to be photographed (fig. 3).

The radiotherapy apparatus is a standard 250 kV unit filtered to give a half-value layer of 1·70 mm. of copper (in treating one of the breast tumours—case 6—this was reduced to 1·15 mm. to get a higher dosage-rate).

To obtain results quickly we tried to determine whether the expected increase in radiosensitivity was demonstrable histologically. To do this we treated patients with carcinomas large enough to be divided into two fields for irradiation. One field was irradiated with the patient breathing air at atmospheric pressure, and the other with the patient breathing oxygen at three atmospheres in the pressure chamber. Each field was irradiated once only with the same dose of X rays. To compare the effect on the two fields a dose was given (1000–1500r at the tumour) which was insufficient to kill all the cells. After an interval a biopsy specimen was taken from each field, or the growth was excised, and the pathologist was told where the dividing line between the fields lay but not which field had been irradiated in oxygen.

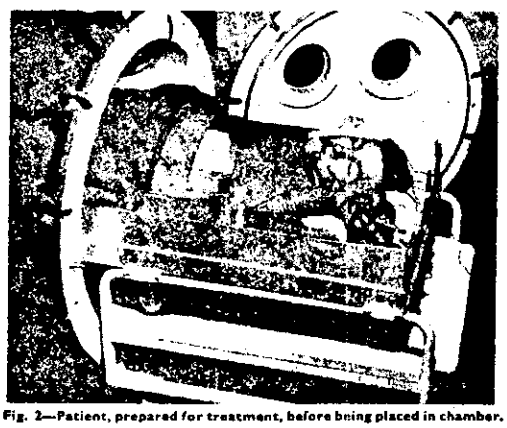

Fig. 2—Patient, prepared for treatment, before being placed in chamber.

Eight patients were treated: four had carcinomas of the lung, and four carcinomas of the breast (two were local recurrences after mastectomy). The breast tumours were treated in two anterior fields and were divided by covering one half with lead sheets.

The lung tumours were treated in directly opposing anterior and posterior fields. To obtain an accurate line of division the patients were screened in the exact positions in which they were to be treated. With the patient supine a wire-mesh grid was placed on the anterior chest wall and adjusted so that the central wire was directly over the proposed line of division. The grid was then outlined on the skin surface with a dye so that it could be replaced in the same position. With the X-ray tube centred over it an anteroposterior picture was taken (fig. 4). The whole procedure was then repeated with the patient prone and the grid on the posterior chest wall, and a postero-anterior film was taken. When the films had been developed, the grids were replaced and the fields marked with any small adjustments necessary.

Procedure

Premedication.—Phenobarbitone gr. 1 was given four hours before treatment, and atropine gr. $^1/_{60}$ with 'Omnopon' gr. $^1/_6$ one hour before treatment. In cases

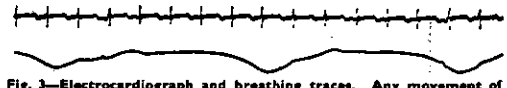

Fig. 3—Electrocardiograph and breathing traces. Any movement of the patient's upper lip will cause an electromyograph trace to be superimposed on the electrocardiogram. The notches in the breathing trace are caused by closure of the valves.

7 and 8 chlorpromazine 50 mg. and pethidine 100 mg. were given intramuscularly instead of omnopon.

Anæsthesia and Myringotomy.—Pentobarbitone sodium in 5% solution was injected intravenously through a Gordh needle at the rate of 1 ml. a minute until consciousness was lost; 0·25 g. usually sufficed, but in one case 0·75 g. was needed. Pethidine 100 mg. was then given slowly through the same needle, followed by succinylcholine 50 mg. In cases 7 and 8 only chlorpromazine 50 mg. was given with the pethidine. The patient's lungs were next inflated with oxygen and, after the trachea and vocal cords had been sprayed with 4% lignocaine, the largest convenient endotracheal tube was passed under direct vision. The tube was secured, and a metal airway of sufficient size to prevent biting of the tube was inserted. Controlled respiration was applied until spontaneous breathing returned; this was done with 75% nitrous oxide and 25% oxygen while the myringotomies were performed. The anæsthetic machine was then disconnected and the patient allowed to breathe air.

Preparation for Treatment.—At this stage the patient was transferred to the pressure-chamber trolley, the carbon-dioxide absorber was connected, and the electrodes were applied to the left leg, upper lip, and right arm. To confine the irradiation to one of the fields at a time the other field and the surrounding skin were covered with lead sheets 2 mm. thick (or equivalent thickness of lead rubber), and the tube was placed so that its central ray passed through the middle of the dividing line. When the patient had been correctly placed in the chamber, the height of the X-ray tube was adjusted so that the anode-skin distance was 60 cm., and the electrical connections were completed.

Compression.—Before the door was closed the chamber was flushed with oxygen to wash out the air. The exhaust

valves were next closed, and oxygen was allowed to flow into the chamber until the required pressure was reached. Compression was carried out fairly slowly to minimise carbon-dioxide retention (Bean 1945) and temperature changes, about 10 minutes usually being allowed.

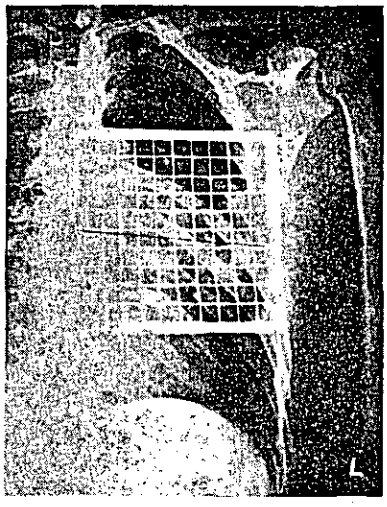

Fig. 4—Anteroposterior radiograph showing wire-mesh localising grid in position. The dark line across the grid is that about which the tumour was divided into two irradiation fields.

Treatment and Decompression.—Treatment took, on the average, 40 minutes for each field. After this the patient was slowly decompressed. In the patients with breast tumours this took about 7 minutes. It could probably be done in less time because "bends" (caisson disease) rarely occur with oxygen, but excessive cooling of the patient might occur. Decompression of patients with lung tumours was done more slowly, taking about 15 minutes. This was because of the risk of damage to the lung beyond a partially blocked bronchus by oxygen remaining at a higher pressure.

Case-reports

Case 1.—A woman, aged 49, had an extensive carcinoma of the left breast, which was swollen, hard, and fixed. There were multiple nodules in the overlying skin and erysipeloid infiltration extending wide of the breast in all directions. Enlarged fixed glands were present in the left axilla and supraclavicular region. The left arm was dusky and swollen, and there were engorged veins around the shoulder.

Treatment.—The breast region was divided transversely just above the nipple into two irradiation fields. The upper field was the larger, having an area of 330 sq. cm., and included the cervico-axillary lymph chain. The lower field was 120 sq. cm. A single dose of 1000r was given to each area, the upper field being irradiated with the patient breathing oxygen at three atmospheres, and the lower field four days later with the patient breathing air at atmospheric pressure.

Result.—The skin reaction in the field irradiated during the inhalation of oxygen was slightly more than that in the field irradiated in air. There was dramatic regression of the tumour in both fields, but clinically there was little difference between them. As swelling diminished, the primary tumour was found to be in the upper and outer quadrant of the breast—i.e., wholly in the field irradiated in oxygen.

Biopsy of each field 14 days after treatment showed skin and a little subcutaneous tissue. There was lymphatic permeation of the dermis, but few tumour cells were present in either specimen. In the tissue irradiated in air there were more undamaged tumour cells than in the tissue irradiated in oxygen, in which there was also more inflammatory response.

Case 2.—A man, aged 61, developed a recurrence of carcinoma of the left breast beside the scar of a radical mastectomy done two years previously. It measured 75 × 67 mm., was fixed to the chest wall, and was fungating through the skin. Lying lateral to it, separated by about 20 mm. of apparently healthy skin, was a nodular skin recurrence 10 mm. in diameter. In addition there were another skin nodule 7·5 mm. in diameter in the medial infraclavicular region and small fixed glands in the left axilla and supraclavicular region.

Treatment.—The main mass was divided diagonally into two irradiation fields, and each was given a single dose of 1000r. One was irradiated with the patient breathing oxygen at three atmospheres, and the other, two days later, with the patient breathing air at atmospheric pressure. The skin nodule lateral to the main mass was treated in oxygen simultaneously with the first field.

Result.—Striking regression of the main mass resulted, but there was little difference in the flattening of the two halves or in the skin reactions.

Biopsy specimens were taken from apparently comparable areas of each field 16 days after treatment. These consisted of skin and subcutaneous tissue with large numbers of tumour cells in the dermis. In the tissue treated in oxygen a higher percentage of tumour cells had been damaged and there was a greater inflammatory response. In the tissue treated in air there were undamaged cells and a few in mitosis.

Skin Nodules.—The skin nodule treated in oxygen had completely disappeared 14 days later. For comparison the nodule in the infraclavicular region, which had not been treated, was allowed to reach a diameter of 10 mm. and then given a single dose of 1000r in air. Three weeks later it had shown only slight regression, then being 8 mm. in diameter.

Case 3.—A man, aged 48, had a large mass in the hilar region of the left lung. The left upper-lobe bronchus on tomography appeared to be completely blocked and the lower-lobe bronchus narrowed. This was confirmed by bronchoscopy.

Treatment.—The growth was treated in one session, each half receiving a minimal tumour dose of 1000r from opposing 8 × 15 cm. fields. The lower half was treated with the patient breathing air, and one hour later the upper half with the patient breathing oxygen at three atmospheres.

Result.—On radiography one and two weeks after treatment there appeared to be a dramatic regression of the tumour. The skin reaction was more marked in the field treated in oxygen, but the difference was not great. Three weeks after irradiation a left pneumonectomy was done. No difficulty which might be considered due to irradiation was experienced.

Operation Specimen.—The tumour was an oat-cell carcinoma arising in the upper-lobe bronchus. With the exception of a few tumour cells in a lymph-node in the hilum, all the cells in both fields appeared to be necrotic.

Case 4.—A woman, aged 55, had had a radical mastectomy for carcinoma of the right breast. No postoperative irradiation was given. For nine years she remained clinically free from recurrence but then began to develop multiple local skin nodules and later glandular metastases. These were treated as they arose, some surgically and others by irradiation. Thirteen years after the mastectomy she developed two skin nodules, each 7 mm. in diameter, 20 mm. apart in previously unirradiated skin.

Treatment.—A single dose of 1500r was given to each nodule, one with the patient breathing air and the other, about half an hour later, with the patient breathing oxygen at three atmospheres.

Result.—Three weeks later there appeared to be slightly more regression of the nodule treated in oxygen, but the difference was not sufficient to be conclusive. There was no difference in the skin reaction in the two areas. The nodules were then excised.

Histology.—In each nodule there were areas of tubular cuboidal and columnar cell carcinoma and no damaged tumour tissue was present. It appeared from serial sections that active growth was taking place in each nodule, but to a lesser extent in the one treated in oxygen, in which there were also more chronic inflammation and fibrosis.

Case 5.—A man, aged 59, had a large mass in the lower lobe of his right lung. It was found on bronchoscopy that the basal branches of the lower-lobe bronchus were completely obstructed by a tumour. This was a poorly differentiated squamous carcinoma.

Treatment.—The growth was divided diagonally into two irradiation fields of equal size. The lower and inner area was treated with the patient breathing air; about an hour later the upper and outer area was treated with the patient

breathing oxygen at three atmospheres. Each area received a minimal tumour dose of 1000r from opposing triangular fields 15 × 15 × 21 cm.

Result.—Radiography 12 days after treatment showed no regression. Sixteen days after treatment a right pneumonectomy was done.

Histology.—The tumour was approximately spherical and 8 cm. in diameter. It occupied most of the lower lobe of the lung and infiltrated the diaphragm and pericardium. But for an incomplete rim of carcinoma 1–3 mm. wide the whole mass was necrotic. *In this rim there appeared to be more irradiation* damage in the upper and outer area.

Case 6.—A woman, aged 57, had a firm tumour measuring 7·5 × 6 cm. in the lower outer quadrant of the right breast. This was fixed to the overlying skin, in which there was a small ulcerated area, and to the underlying muscle. There was also extensive infiltration of the surrounding skin.

Treatment.—The tumour was divided into two fields for irradiation in a sagittal plane. The lateral field, which measured 10 × 15 cm., was irradiated with the patient breathing air. About an hour later the medial field, which measured 12·5 × 15 cm., was treated with the patient breathing oxygen at three atmospheres. A single dose of 1500r was given to each area. Owing to the rounded contour it was impossible to avoid a small area in the centre of the main mass receiving irradiation from both fields, but this was minimised by leaving a gap of 1 cm. between the adjacent edges of the two fields.

Result.—A local mastectomy was done 10 days after irradiation. At this time there was no obvious regression in either half of the tumour, and the skin reaction, a mild erythema, was similar in each irradiation field.

Histology.—*The main tumour mass measured about 3 × 3 cm., and 1·5 cm. between the retracted skin and muscle.* It was an acinar polygonal-cell carcinoma in which a few tubules lined by columnar cells had been formed. There was extensive infiltration of the dermis beyond the main mass. The most severe damage caused by irradiation had occurred in the primary tumour close to the dividing line between the irradiation fields. Tumour cells in the dermis in the field *treated in oxygen had been damaged by irradiation. There* was some damage, probably less, to tumour in the region thought to have been treated in air only, but this was too near the line of division for us to be sure that it was not affected by the overlapping of the fields.

Case 7.—A man, aged 48, had in the hilar region of his left lung a large mass which had obstructed the origin of the upper-lobe bronchus.

Treatment.—The tumour was divided transversely for irradiation, each half receiving a minimal tumour dose of 1000r from opposing fields measuring 7·5 × 15 cm. The lower half was treated with the patient breathing air, and then about an hour later the upper half with the patient breathing oxygen at three atmospheres.

Result.—Radiographs, including tomograms, taken 11 days after treatment showed much regression of the growth but no demonstrable difference between the amounts in the two areas. Thirteen days after irradiation a left pneumonectomy was done.

Histology.—The tumour arose in the lingular branch of the upper-lobe bronchus and measured about 25 × 15 × 15 mm. There was extensive infiltration of the hilar lymph-nodes, the walls of the upper-lobe and lower-lobe bronchi, and the adjacent lung tissue. The tumour was a poorly differentiated round-cell and polygonal-cell carcinoma. In the central portion, about the dividing line, was much necrosis. In comparable fields near the upper and lower limits of irradiation was much more damage to the tumour cells in the upper part, which was irradiated in oxygen.

Case 8.—A man, aged 62, had a mass in the hilum of his left lung with consolidation of much of the lung distal to it. The mass was found to be a poorly differentiated squamous carcinoma.

Treatment.—The tumour was divided transversely for irradiation, each half receiving a minimal tumour dose of 1000r from opposing fields measuring 10 × 12 cm. The lower half was treated with the patient breathing air, and the upper half about an hour later with the patient breathing oxygen at three atmospheres.

Result.—Radiography a week after treatment showed no material change. Ten days after treatment thoracotomy was done. A large growth at the hilum was found to be inoperable because of extensive involvement of the aorta.

Biopsy specimens were taken from the upper and lower halves of the growth. These contained small amounts of acinar and trabecular squamous carcinoma. There appeared to be more irradiation damage in the specimen from the upper half.

Results

Satisfactory, though experimental, apparatus and technique have been developed for the irradiation of patients breathing oxygen at high pressures.

Eight patients were treated without mishap or complication attributable to the treatment.

The pathologist was not told which part of the tissue had been irradiated in air and which in oxygen. In six cases (1, 2, 4, 5, 7, and 8) the tissue which he reported to be the more damaged was that irradiated in oxygen. This was also probably true of case 6, but the conditions of the experiment were not fulfilled, the pathologist having been told, because of some misunderstanding about the dividing line, which tissue was which. In case 3 no distinction was made because none of the tumour cells in either field had survived.

Discussion

Empirically oxygen is known to enhance the damage caused by irradiation, and, although the mechanism is not understood, some possibilities have been discussed (Gray 1953). The relation between the tension of oxygen dissolved in the environment of the cells and the degree of damage which occurs follows a common pattern in plants and animals, both in vivo and in vitro. Graphically this relationship is represented by a curve rising steeply from zero and then flattening out suddenly as the sensitivity to irradiation almost ceases to be affected by any further increase in oxygen tension. During the rise the sensitivity of the cells is increased by three times. From this it would be expected that tissues with poor blood-supply would be much more affected by irradiation with oxygen than would normally oxygenated tissues.

Since there are areas in almost every malignant tumour where there is necrosis caused by poor circulation, there are likely to be areas of living cells in various degrees of oxygen deficiency. It is postulated that the respiration of oxygen will increase the sensitivity of these cells to *irradiation damage and so produce a relative increase in* the amount of damage to the tumour as a whole compared with normal tissues. As a corollary it is also postulated that, if poorly oxygenated cells survive the maximal doses of X rays tolerable in normal practice, they would, because of the inflammation following death of the better oxygenated tumour cells, receive a blood-supply sufficient *for them to continue to multiply.*

The work done by Gray et al. (1953) on irradiation during respiration of high-pressure oxygen was confined to plants and laboratory animals. Their results were sufficiently encouraging to warrant an early trial in man. Many investigations are being conducted with oxygen at one atmosphere, and at least one encouraging report has been published (Hultborn and Forssberg 1954). We felt that information was urgently required about the effects of irradiation in patients breathing oxygen at three atmospheres.

This pressure has been used experimentally, but there is as yet no definite evidence that it is ideal in any particular tumour. It seems likely that different pressures will be required to produce the optimal results in tumours with different circulatory conditions.

In the treatment of our patients we have assumed with Gray that, to be effective, oxygen and irradiation must be administered simultaneously. We are aware that it has been suggested (Gerschman et al. 1954) that oxygen poisoning and the effects of irradiation have a mechanism in common, which may be cumulative even if the oxygen is breathed within a few hours after irradiation.

We have explained as fully as possible the experimental nature of the treatment to each of our patients and have obtained from each specific permission to do all that we intended. In selecting patients for treatment, care was taken to choose only those with advanced disease. In cases 3, 5, 6, 7, and 8 the surgeon considered the growth to be of doubtful operability, and in these the irradiation was given as a preoperative measure. In cases 1, 2, and 4 the presence of metastases made palliative irradiation the only possible treatment.

The apparatus we have used is experimental and has its limitations; for instance, it is only possible to treat tumours in the upper half of the body, and only one field at a time can be treated without decompressing and moving the patient. Although the procedure has been safe, it has been tedious and time-consuming, taking up to six hours for a single patient. This, however, was partly due to our treating the tumours in two separate operations, and partly to the low output of our X-ray unit.

As regards anæsthesia, the main problem has been to keep the patient safely anæsthetised for a long period during which he was inaccessible to the administration of further drugs. Pentobarbitone sodium was suitable for this purpose as well as for delaying convulsions, but the necessity for using an endotracheal tube to guarantee an airway caused difficulty due to coughing. This could not be overcome by local anæsthetic or cough-depressant drugs. Therefore in later patients chlorpromazine has been added although it is known that this may alter circulation-rates in the tissues; this factor, however, is probably not important. Chlorpromazine has the advantage of being itself a protection against oxygen convulsions (Paton 1955).

The prevention of carbon-dioxide accumulation in the chamber is of great importance, because the inhalation of even small percentages of this gas accelerates the onset of oxygen convulsions. It is essential that all expirations be passed through an absorber. To avoid inspiratory resistance two one-way valves were used which enable the patient to breathe in directly from the surrounding atmosphere and out through the absorber. Since the thermistor only gives the respiratory rate, we hope in future to get additional information by incorporating a microphone in the endotracheal tube. The anæsthetic problems and technique are discussed in detail elsewhere (Sanger et al. 1955).

The anæsthetic was completely effective in preventing convulsions, and no late complications were experienced. The patients were warned of possible slight temporary loss of hearing after treatment. In practice this was minimal and did not usually last more than twenty-four hours. Since each patient was only treated in the pressure chamber once, the polyethylene tubes used to keep the myringotomy perforations patent were removed immediately afterwards. If it were intended to give serial treatments they could, however, be left in situ for several weeks without ill effect.

Because of the dose given and the area treated radiation sickness was anticipated. Therefore dimenhydrinate 100 mg. and pyridoxine 20 mg. were given three times daily for five days, and no radiation sickness developed. In case 7, to ascertain whether oxygen was protecting against sickness, we omitted these drugs, and moderate radiation sickness resulted.

The difficulty of obtaining a sharp dividing line between the two irradiation fields in lung tumours has limited us to treating comparatively large growths. In spite of the precautions taken we have assumed, when taking biopsy specimens or examining the whole specimen, that there was an area of overlap and confined our attention to areas of the tumour farthest from the dividing line. The whole object of the histological examination was to see if there was a recognisable difference between tumour tissues treated in the two different ways. The main difficulty was to ensure that the areas examined were as far as possible comparable. In some cases the pathologist selected the tissue irradiated in oxygen from the appearance of the tumour cells alone, but in others indirect evidence, such as the degree of inflammatory reaction, was taken into account. Because of this the reasons for the selection in any single case are open to criticism, but the total result of the selections sufficiently suggests an increased effect of irradiation in oxygen to warrant a more extensive trial.

It will be noted that the interval between treatment and either biopsy or excision of the tumours varied between one and three weeks. We are now of the opinion that, when using doses designed to leave some viable cells, the best time to assess the damage is from seven to ten days after treatment. Assessment later than this may be more difficult because surviving cells will have had time to produce fresh islets of growth—e.g., case 4.

We do not think that more conclusive evidence can be obtained from proceeding along these lines, and therefore we have planned a controlled trial using potentially curative doses to the whole tumour. In this we also hope to ascertain the optimal pressure of oxygen, though this is likely to vary for different tumours. The work of Howard-Flanders and Wright (1955) suggests that, with irradiation to high dosage, the addition of oxygen may bring an increased liability to bone necrosis owing to its normally poor oxygenation. This difficulty is likely to be overcome when higher-energy irradiation becomes available, because this is less absorbed by bone.

Summary

A preliminary investigation was made in which eight patients with carcinomata were given radiotherapy while breathing oxygen at three atmospheres absolute.

Satisfactory, though experimental, apparatus and technique are described.

The results sufficiently suggest an increase in the radiosensitivity of tumours so treated as to warrant a more extensive trial.

We express our gratitude to Sir Robert Davis, without whose generosity in providing the pressure chamber this investigation would not have been possible; Dr. L. H. Gray, Dr. O. C. A. Scott, Dr. J. A. C. Fleming, Mr. G. H. Bateman, Dr. H. J. Taylor, the surgeons and diving officers of H.M.S. *Vernon* and H.M.S. *Reclaim*, Dr. A. Glücksmann, Dr. F. G. Spear, Dr. P. Brauwens, Dr. G. L. Gryspeerdt, Dr. A. H. Galley, Mr. P. Styles, Mr. P. Tothill, Mr. A. E. Clark, Mr. H. C. Davies, the British Oxygen Company, and the staff of Siebe Gorman Ltd. for their assistance; Mr. G. Kent Harrison, who operated on the lung tumours; Mr. J. Kodicek and the staff of the ear, nose, and throat department who performed the myringotomies; Mr. T. W. Brandon for the photographs; and the staff of the radiotherapy department for treating these patients in their off-duty hours.

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J. PHYSIOL. 18:201-217, 1895

THE RELATION OF THE ACTION OF CARBONIC OXIDE TO OXYGEN TENSION.

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The following investigation took its origin from an enquiry in which I am at present engaged into the nature and action of the suffocative or poisonous gases met with in the air of coal-mines. Among these gases is carbonic oxide. So far as my experience goes, however, carbonic oxide never occurs alone as an impurity, but always in connection with an excess of diluent gases, chiefly nitrogen; so that when carbonic oxide is present in the air of a coal-mine, there is also a more or less considerable reduction in the percentage of oxygen. It is known, however, firstly, that part at least of the action of carbonic oxide is due to its property of entering into combination with the hæmoglobin of the blood corpuscles, and so putting them out of action as oxygen carriers; and, secondly, that the proportion of carbonic-oxide-hæmoglobin formed in blood brought into contact with a gas-mixture containing carbonic oxide and oxygen, depends not merely on the tension of carbonic oxide in the mixture, but also on the tension of oxygen. The larger the proportion of oxygen in the gas mixture the smaller will be the amount of carbonic-oxide-hæmoglobin formed in the presence of a given proportion of carbonic oxide. Hence it might be expected that in air containing a diminished proportion of oxygen, carbonic oxide will be more poisonous; and that in air containing an increased proportion the poisonous action will be less.

A very simple experiment served to show that this is the case.

Two bottles, each of about three litres capacity, were filled, one with oxygen, and the other with air. Into each bottle 15 c.c. of carbonic oxide were introduced through a tubulated stopper. The bottles were then closed, and the gases mixed by thorough shaking with a little water which had been left for the purpose inside. The water having been removed a young mouse was introduced into each of the bottles, which were again closed. Within

five minutes the mouse in the bottle containing air showed marked signs of loss of power over the limbs, and two minutes later it was lying on its back comatose. Fresh air was then at once blown through the bottle with a bellows. Two minutes later the mouse had regained power over its limbs, and about twelve minutes later it seemed quite in its normal condition again. Meanwhile the mouse in the bottle containing oxygen remained quite unaffected. After an hour and a half it was taken out. For some time previously it had been shivering, and was evidently suffering from cold, as it had got rather wet in the bottle, but it showed no symptom of poisoning. Both mice remained perfectly well when replaced in their cage.

It seemed of importance to determine as accurately as possible within what limits raising or lowering of the oxygen percentage affects the poisonous action of carbonic oxide. For this purpose the following arrangement was employed (Fig. 1).

A mouse was placed in the bottle *A*, which had a capacity of about 200 c.c.: through this bottle a perfectly steady air-current in the

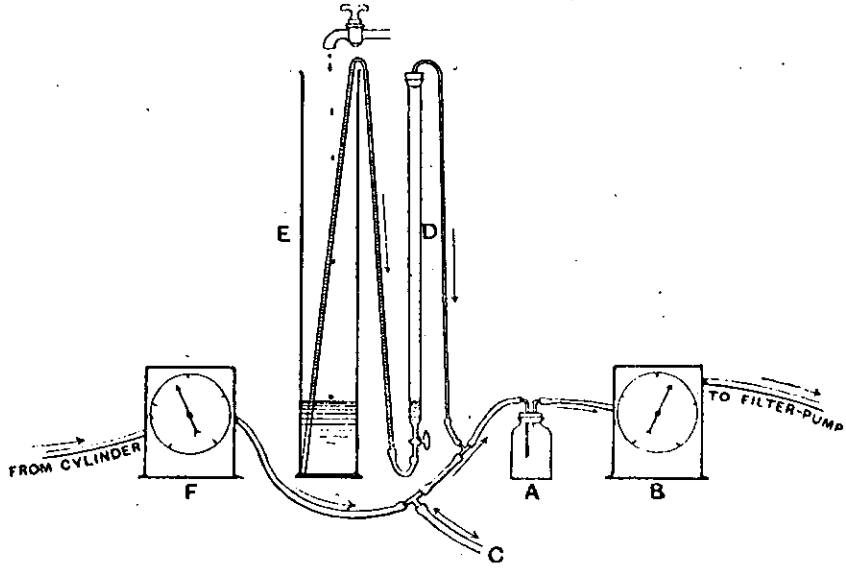

FIG. 1.

direction shown by the arrows was maintained by means of a filter pump driven by water supplied at a constant pressure from a cistern. The air current was measured by the small meter *B* (the accuracy of which was ascertained) and was drawn into the tubing at the opening *C*. Between *C* and *A* a T tube was placed, communicating by one of

its limbs with narrow glass tubing, which was connected in the manner shown by means of a paraffined cork with the upper end of a burette *D*, containing carbonic oxide. The nozzle of the burette was connected with a siphon, dipping into a tall glass jar *E*. Over this jar was a water tap. When water was allowed to drop from the tap into the jar the level of the water in the latter, and in the burette gradually rose, and a measured quantity of carbonic oxide could thus be steadily and slowly driven from the burette into the air current. By regulating the water-tap the rate of outflow of carbonic oxide could be regulated at will. The water-tap was not connected directly with the burette because a steady outflow of water could not be obtained unless the rate of flow was considerable.

When it was desired to substitute oxygen or any other gas for the whole or part of the air the oxygen was allowed to pass in from a cylinder of compressed gas through the meter *F*. When pure oxygen was required the flow was so regulated that a slight excess of oxygen passed outwards by the opening *C*. By means of this arrangement it was possible rapidly to substitute oxygen for air without the slightest interruption or alteration in the rate of flow through the bottle and meter *B*.

The carbonic oxide employed was made in fairly large quantities at a time by heating oxalic acid with sulphuric acid, and kept in a large bottle fitted up as a gasholder. The gas was purified by passing it through a large tube of moist potash-lime. Each new stock of carbonic oxide was accurately analysed to ascertain the degree of purity of the gas. Sometimes, as in the example given below, it was found that, in spite of care, appreciable quantities of air had become mixed with the carbonic oxide. In calculating the percentages allowance was in each case made for the impurity. The oxygen was determined with pyrogallic acid and potash, and the carbonic oxide by ammoniacal solution of cuprous chloride. The apparatus was the same as that which I have used in the analysis of gases from coal-mines.[1]

Example of an analysis.

Carbonic oxide	92·27	
Carbonic acid	0·07	
Oxygen	1·56	= 7·66 of air.
Nitrogen	6·10	
	100·00	

[1] *Proc. Roy. Soc.* 57, p. 244, 1895, and *Transactions of the Federated Institution of Mining Engineers*, 1895.

A month later, after nearly the whole of this bottleful of gas had been used, the residue was found to contain 0·15 % of carbonic acid and 1·96 % of oxygen (corresponding to 9·4 % of air), so that there was only a very slight additional contamination of the gas by air diffusing from the water.

As good reasons exist for suspecting that the gas employed in some of the recorded experiments on carbonic oxide was impure and contained carbonic acid or air, it seemed necessary to take every precaution as regards the gas employed.

In air about 0·06 % of carbonic oxide is sufficient to produce distinct symptoms in mice. The following are the notes of an experiment.

Young black and white mouse about half grown. Rate of ventilation 1·70 litres per minute. Rate of CO delivery 1·00 c.c. per minute. Corrected percentage of CO = ·058 %[1]. Temperature 13° C.

5 p.m. Mouse placed in bottle and left in the air current, no CO being added.

5.38 No change. Quite active. Movements as sharp as usual. Climbs up glass tube, cleans its fur, &c. as usual. CO now added.

5.42 Slight hyperpnœa, the respiratory movements being more visible.

5.47 Mouse less active. Sits up on hind legs, panting slightly. Does not clean its fur, &c. as usual.

5.51 CO off.

5.57 Cleaning its fur vigorously, climbing up the tube, and is altogether much more lively. No longer panting, and appears to be quite as usual again.

5.59 CO again started.

6.4 Panting distinctly. On trying to climb up it gets exhausted, and sits panting.

6.13 Remains very quiet. Sitting in one position, and apparently panting.

6.24 Seems drowsy and torpid. When roused so that it tries to climb up the glass a tendency to slip down is apparent, so that there is some loss of power in the limbs.

6.30 Bottle containing mouse was put in warm water at about 35° C.

6.35 Panting much less, but torpor and feebleness remain.

6.36 Bottle put in cold water at 12°. Panting began again in about a minute.

[1] The stock of carbonic oxide used in this experiment had the following composition:

Carbonic oxide	97·42	
Carbonic acid	0·05	
Oxygen	0·48	air 2·53.
Nitrogen	2·05	

6.55 After the last observation had been repeated several times the bottle was placed in warm water at 26° and left.

7.6 Quite as torpid and feeble as ever. CO off.

7.12 Has regained its full power over limbs, climbed up tube without exhaustion, and then began to clean its fur.

7.15 Quite as lively as usual again.

The following experiment will afford an idea of the effects of a somewhat higher percentage of carbonic oxide.

Young mouse, not quite fully grown. Rate of ventilation 1·03 *litres per* minute. Rate of CO delivery 2·34 c.c. per minute. Corrected percentage of CO 0·221 %. Temperature 14·5°.

10.55 CO started.

10.59 Hyperpnœa and great loss of power over legs. Cannot stand. Lies on belly with legs stretched out. Seems hardly conscious.

11.12 Continues very helpless and drowsy looking. Remains lying on side when put there, but does not remain on its back.

11.20 Same condition, but respirations seem less frequent (108). [Normal frequency = about 140.]

11.35 Respirations 90. Seems feebler.

11.46 Respirations 74 and are feebler. Remains on back when put there.

11.57 Respirations 66. Has lain on its back since last observation.

12.8 Respirations 44.

12.27 Respirations 35.

12.49 Respirations 16 and gasping in character.

1.20 Died almost imperceptibly. Since last observation respirations had gradually become shallower, until at last they died away.

On post mortem examination the liver and other organs had the characteristic bright red appearance seen in carbonic oxide poisoning. On diluting a little of the blood with water the colour of the solution indicated that the blood was about two-thirds or three-fourths saturated with CO.

With larger proportions of carbonic oxide than in the last experiment death is correspondingly more rapid, and is accompanied by convulsions, as in the case of asphyxia from breathing an atmosphere deprived of oxygen. If death occurs within a few seconds the blood in some parts of the body may, as Heger has already observed[1], contain very little carbonic oxide hæmoglobin, death being too rapid to allow the whole of the blood to become saturated.

The observation that so small a proportion 0·06 % of carbonic oxide

[1] *Journal de Médecine de Chirurgie et de Pharmacologie*, 1894, p. 106.

produces distinct symptoms is not new, but has previously been made by Hempel.[1]

It is probable that, particularly with such small animals as mice, death by poisoning with very small proportions of carbonic oxide is due partly to fall of the body temperature consequent on diminished metabolism and heat production. The following experiment, in which the production of carbonic acid by a mouse was estimated, supports this view.

The apparatus was the same as that already described (fig. 1) except that the air entering the bottle was deprived of carbonic acid by soda lime, while the carbonic acid in the outgoing air current was estimated by means of the absorption apparatus described by Mr Pembrey and myself[2].

Time	CO_2 given off in grammes	Air breathed by mouse
First 15 minutes	·0552	Pure air
Second ,, ,,	·0570	Pure air
Third ,, ,,	·0531	0·16 % of CO
Fourth ,, ,,	·0264	0·16 % of CO
Fifth ,, ,,	·0272	0·16 % of CO
Sixth ,, ,,	·0227	Pure air
Seventh ,, ,,	·0405	Pure air
Eighth ,, ,,	·0508	Pure air

The carbonic oxide produced the characteristic loss of power over the limbs, &c. Recovery was rather slow. During the seventh and eighth periods shivering was observed, as if the animal were suffering from cold. Probably its temperature had gone down under the influence of the carbonic oxide. The bottle containing the animal was kept in a bath at 15·5° C., and the rate of ventilation was 0·48 litres per minute.

It will be seen that the carbonic oxide produced a very marked diminution in the respiratory exchange, and that the diminution lasted for about half-an-hour after the animal had ceased to breathe the carbonic oxide.

Experiments with Carbonic Oxide in Oxygen.

The oxygen used in these experiments was that supplied in cylinders by Mr Orchard. It contains about 97 % of oxygen. The

[1] *Zeitschrift für analytische Chemie*, XVIII. p. 399.
[2] *Philosophical Magazine*, 1890, p. 306.

following is the result of an analysis of a sample from the cylinder employed in most of the experiments.

Oxygen	96·91
Carbonic acid	0·25
Nitrogen	2·84
	100·00

I have breathed this oxygen pure for considerable periods without its producing any appreciable effects. It has no smell suggestive of chlorine or other impurity.

In oxygen it requires about ·8 % of carbonic oxide to distinctly affect a mouse, and very much more to produce death. The effect of dangerous percentages (over 5 %) seems to vary considerably according to circumstances. When the percentage is gradually increased the mouse appears to be capable of adapting itself to a considerable extent to the atmosphere. The following two experiments may be quoted.

Young mouse, not quite fully grown. Initial ventilation ·28 litres per minute. Bottle kept in bath at 28°.

12.20 Mouse put in bottle and ventilated with oxygen.
12.37 CO started. Corrected percentage = ·85.
12.41 Slight hyperpnœa, and seems a little drowsy.
12.46 *Distinct sluggishness, and apparent slight loss of power, noticed* when it jumps up on the side of bottle.
12.55 Condition same. Ventilation reduced, so that CO percentage = 1·76.
12.58 Hyperpnœa and marked loss of power. On trying to climb up it stops to rest, or slips down.
1.5 Seems no worse. Lies or sits in awkward positions, as if very drowsy. When roused gets up on legs.
1.14 No worse. Began to clean its fur, but stopped again at once.
1.20 Ventilation increased from ·13 to ·66 litres per minute (i.e. to five times its previous amount). Oxygen turned off and air substituted. Percentage of CO now = ·34 (i.e. a fifth of its former amount.)
1.22 Seems decidedly more feeble, and rapidly losing power.
1.25 Remains lying on its side or back in a comatose state.
1.26 CO exhausted. The mouse had recovered completely a few minutes later.

Same mouse. Ventilation throughout = ·102 litres per minute. In bath at 28°.

2.5 Mouse put in and ventilated with pure oxygen. After a short time went to sleep.

2.12 CO started. Percentage = 2·31.
2.15 No change in the mouse. Sitting asleep.
2.17 Laying head down; seems unnaturally drowsy and losing power over limbs.
2.22 Lies with legs spread out, but will not remain on its back.
2.28 Condition same. CO increased to 2·97 %.
2.39 Not apparently more feeble. Still will not lie on its back. Sometimes wakes up and tries to climb.
2.41 CO increased to 7·2 %.
2.47 Still does not remain on its back, and seems no worse. CO exhausted.
3.0 Completely recovered. Now cleaning its fur.

These experiments sufficiently show that in oxygen carbonic oxide is very much less poisonous than in air. This fact can also be very conveniently demonstrated with the apparatus described by alternately supplying the animal with air and oxygen, while the delivery of carbonic oxide and the rate of ventilation remain absolutely unaltered. If about ·2 to ·5 % of carbonic oxide are added to the ventilating current the animal will be seen to alternately become worse or recover again according as air or oxygen is supplied. With a somewhat higher percentage death occurs very rapidly when air is supplied.

Experiments with diminished oxygen percentages.

To obtain an atmosphere containing a diminished percentage of oxygen, hydrogen or nitrogen was partially substituted for air by means of the arrangement already described. The hydrogen employed gave no arsenic reaction with Marsh's test, and portions from the same cylinder had previously been used for experiments on man without any ill effects being produced.

Mice, as compared with men, appear to be specially sensitive to reduced percentages of oxygen. A mixture of one-third of hydrogen, or nitrogen and two-thirds air causes panting and uneasiness. Cyanosis and loss of power over the limbs is caused by a mixture containing two-thirds of hydrogen. With considerably reduced percentages of oxygen it is thus difficult to distinguish the symptoms produced simply by lack of oxygen from those due to carbonic oxide. Nevertheless it is quite evident that the poisonous action of carbonic oxide is very markedly increased by a diminution of the oxygen percentage. The following experiment may be quoted.

Half-grown brown mouse. Ventilation 1·00 litres per minute. Temperature 12·5°.

1.7 Mouse put into bottle and ventilated with pure air.
1.9 *Continues quite lively.* Hydrogen now added at the rate of ·33 litres per minute, so that oxygen percentage was reduced from 20·9 to 13·9.
1.12 *Mouse panting a little, and is not so lively.* Still cleans its fur, &c. but often stops to pant.
1.21 Mouse remains the same. No loss of power. Hydrogen off.
1.24 Panting ceased. *Much more lively.*
1.25 CO turned on. Percentage = 0·247.
1.27 Panting.
1.29 Limbs getting feeble.
1.32 Limbs sprawling. Mouse sits resting on its belly. Will not lie on side or back.
1.35 No further appreciable change in mouse. Hydrogen turned on at same rate as before.
1.36 Mouse much worse. Lies on back.
1.36½ Respirations gasping in character. Mouse lying on back with limbs twitching.
1.38 Seems to be dying. Hydrogen off.
1.39 Improving. Will not now lie on back. Twitching and gasping respirations have disappeared. Limbs still sprawling.
1.40½ Hydrogen on again.
1.41½ Gasping respirations.
1.42½ Remains on back or side. Quite comatose.
1.46 Hydrogen off.
1.51 Remains in same condition. Respirations getting less frequent, CO stopped.
1.58 Still quite comatose. Taken out. Felt very cold, therefore warmed in the hand, when it gradually began to revive, and was replaced in its cage in cotton-wool.

At 2.50 it was still feeble, but when seen again eight hours later it was perfectly well.

A similar very marked increase in the poisonous action of carbonic oxide was observed in several other experiments with hydrogen and air: also in an experiment in which a mixture of 31·4 % of pure nitrogen and 68·6 % of air was employed.

The conclusions drawn from these experiments with carbonic oxide in air containing a reduced percentage of oxygen have of course a special practical interest in connection with carbonic oxide poisoning as

it occurs in coal-mines and elsewhere, but I hope to deal more fully with this subject in another paper.

Discussion of the Results.

In the case of pure oxygen the tension of oxygen is nearly five times as great as in air, so that to produce equal saturation of the hæmoglobin of the corpuscles with carbonic oxide in oxygen and in air, the tension of carbonic oxide would presumably require to be five times as great in the oxygen as in the air. Hence on the hypothesis on which the investigation started one might expect that carbonic oxide would turn out to be about five times as poisonous in air as in oxygen—that is to say, that five times as high a percentage of carbonic oxide would be required in oxygen to produce the effect of a given percentage in air.

Now the experiments made with the apparatus described above clearly showed that carbonic oxide is much more than five times as poisonous in air as in oxygen. In the latter gas the poisonous action is reduced to about a tenth or less. Evidently then some other factor has to be taken into account besides the relative tensions of oxygen and carbonic oxide. That this factor exists was further shown by the following experiment:

A thick-walled bottle of 3·1 litres capacity was filled over water with oxygen, to which was added 30 c.c. of carbonic oxide, so that the oxygen contained about 1 % of carbonic oxide. After the latter had been thoroughly mixed with the oxygen a full-grown mouse was placed in the bottle, which was again tightly closed by means of a tubulated cork, the tube of which was connected with a filter-pump and gauge, so that the pressure in the bottle could be reduced as required. By means of a clamp the bottle could be shut off from the pump when any desired pressure was obtained.

4.40 Mouse put into bottle.
4.42 Some hyperpnœa.
4.56 No further change. Walks and climbs about normally. No distinct loss of power over limbs, though perhaps a little sluggish.
4.56–57 Pressure reduced to about 50 % of an atmosphere.
5.1 Hyperpnœa more marked. More tendency to stop and pant.
5.5 No further change. Pressure reduced to 27 % of an atmosphere.
5.8 Panting greater. Looks drowsy and totters when walking.
5.11 Marked weakness of limbs. Tends to sprawl on its belly or lie on its side but can creep about when roused.

5.15 No further change. Pressure reduced to about 17 % of an atmosphere.

5.20 No marked change. Pressure reduced to about 10 % of an atmosphere.

5.25 Perhaps a little more helpless, but no marked change. Air was now let in to atmospheric pressure, when the mouse rapidly improved, and recovered completely on being taken out.

In this experiment the oxygen tension and carbonic oxide tension were diminished simultaneously, and in equal proportions. The effect of the carbonic oxide nevertheless increased.

To account for this relation between oxygen tension and the effect of carbonic oxide the hypothesis suggested itself that the higher the oxygen tension the less dependent an animal is on its red corpuscles as oxygen carriers, since the oxygen simply dissolved in the blood becomes considerable when the oxygen tension is high.

Experiments with increased Oxygen Pressure.

If the above hypothesis were correct one would expect to find that by raising the oxygen tension sufficiently high it would be possible to abolish entirely the poisonous action of the carbonic oxide. There is, however, a limit to the possibility of raising the oxygen tension, since, as shown by Paul Bert, at about five atmospheres, or somewhat less, oxygen acts as a poison. The question therefore was whether at a less tension than this the action of carbonic oxide could be abolished. To investigate this the following arrangement was employed (Fig 2).

Three thick-walled measuring cylinders, *A*, *B*, *C*, each of about 650 c.c. capacity, and provided with tightly fitting paraffined corks, tubulated in the manner shown, were connected together by means of thick-walled rubber tubing. *A* was further connected, in the manner shown, with a cylinder of compressed oxygen, and a mercury pressure gauge *E*, and with the vessel *C*. Screw clamps were placed on the tubing at *E* and *F*, and there was a three-way glass tap at *D*. The joints, corks, etc. were carefully secured, so as to withstand the required pressure. The vessel *B*, having been first filled with water, was connected with the gas-holder of carbonic oxide, and filled with carbonic oxide, the water being sucked over into *C*. The tap *D* was then closed. A mouse was now placed in *A*, which had been previously filled with oxygen. The cork having been pressed home and secured, the pressure in the whole system was gradually raised to the required amount by

cautiously turning the regulating screw of the oxygen cylinder. The clamp *E* was now closed, and *D* turned so as to connect *A* with *B*. Carbonic oxide could then be driven from *B* into *A* as required, by means of pressure from the oxygen cylinder.

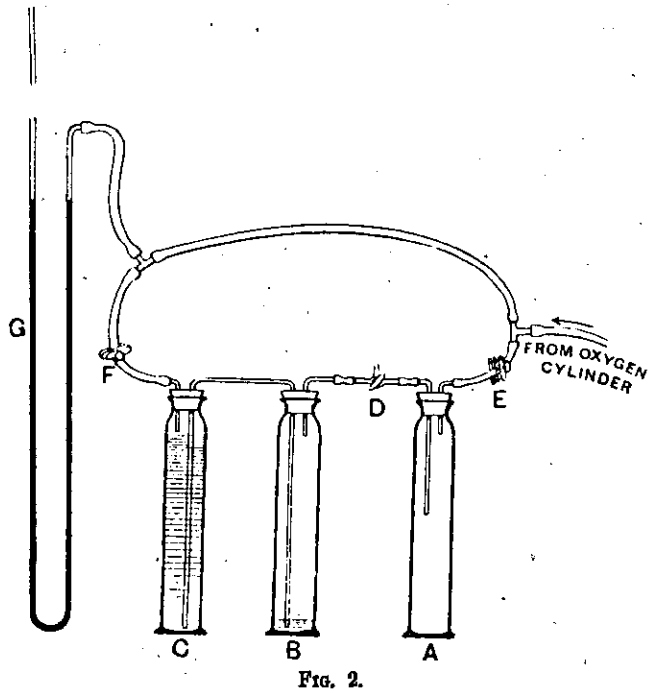

FIG. 2.

The following are the notes of an experiment.

7.15 Large mouse put in.
7.21 Pressure raised to 70·5 cm. of mercury.
7.26 Mouse unaffected. Apparatus tight. 30 c.c. of CO (giving a tension of 6 % of an atmosphere of CO in *A*) driven into *A*.
7.28 Slight hyperpnœa.
7.29 35 c.c. of CO sent in, so that tension of CO in *A* about 15 % of an atmosphere.
7.31 Hyperpnœa more marked. Often jumps up in vessel, as if uneasy.
7.32 50 c.c. of CO sent in so that CO tension in *A* = about 27 % of an atmosphere.
7.35 Mouse gets easily exhausted after any effort, such as jumping up in the bottle. 75 c.c. of CO sent in, so that tension of CO in *A* = nearly 50 % of an atmosphere.

7.38 Mouse as before; can walk about quite well when *A* is held horizontally, but is exhausted easily by any effort. The whole of the CO now sent in, *D* and *F* closed and *E* opened. Pressure in *A* = 139·5 cm., so that tension of CO in *A* = 139·5 – 70·5 = 69 cm., or nearly an atmosphere.

7.47 No change in mouse. Walks about, and climbs on the tube when *A* is held horizontally, but is easily exhausted and somewhat sluggish.

7.47–49 Pressure in *A* diminished to 63 cm. by opening *D* outwards. Mouse rapidly became helpless and unconscious, and began to gasp. Died at 4.51.

Post-mortem. Liver and other organs bright red. A drop of blood largely diluted with water gave the characteristic cherry-red colour, which was hardly appreciably altered on shaking some of the solution with coal-gas. The blood was thus practically saturated with carbonic oxide.

This experiment shows that at a tension of two atmospheres of oxygen the poisonous action of carbonic oxide on mice is abolished. Apart from its action in putting the red corpuscles out of action as oxygen carriers carbonic oxide would thus appear to be a physiologically indifferent gas, like nitrogen[1].

I have several times repeated the experiment just described, but have never found it fail. In some experiments the mouse was kept for half-an-hour or more in the vessel, until the carbonic acid tension must have been nearly great enough to affect the animal.

It might be thought that the death of the mouse is perhaps due to the liberation of gas within its body, from too sudden diminution of pressure. Control experiments with pure oxygen or air showed, however, that this is not the case. Even a very sudden diminution of pressure, from giving way of a cork, did not injure the animal. Diminution of the pressure of a mixture of oxygen with a third of carbonic oxide does not, however, always kill a mouse, as shown by the following experiment.

A young half-grown mouse had been kept since 1.25 at a pressure of 128 cm. of mercury in an atmosphere consisting of about two-thirds of oxygen and one-third of carbonic oxide. At the end of this time it remained quite lively.

[1] Experiments interpreted as leading to an opposite conclusion have been recently described by Marcacci (*Archives Italiennes de Biologie* XIX. p. 205, 1893) and Piotrowski (*Archiv f. Anat. and Physiol.* 1893, p. 205). Neither of these authors, however, furnishes analyses of the gas employed by them, or any other guarantee of its freedom from such probable impurities as carbonic acid and air.

1.49 Pressure reduced to 106 cm.
1.50 Decidedly worse. Legs tend to sprawl.
1.52 Pressure reduced to 78 cm.
1.55 Lying with its head on the bottom of the jar, but does not remain on its back when put there.
1.57–2.8 Pressure gradually reduced to 0.
2.15 Mouse more torpid, but still does not remain on its back. Removed from the glass vessel and brought into the air. Immediately got worse. Lay on its back and had slight convulsions. Breathing ceased at 2.16 except for occasional gasps. Appeared once or twice to be dead.
2.18 Respirations becoming more frequent.
2.23 Still unconscious and does not move limbs.
2.27 Shows signs of returning consciousness, and power over its limbs.
4 p.m. Completely recovered.

Young mice are probably more capable of resisting asphyxia from carbonic oxide poisoning than older ones. This is what might be expected from the fact that young animals are difficult to drown, and may live for a short time in an atmosphere deprived of oxygen.

To remove a mouse with safety from the atmosphere of carbonic oxide in the pressure apparatus it is necessary to replace the carbonic oxide by oxygen without in the operation letting the pressure down to less than about two atmospheres. When the carbonic oxide has been washed out the animal can be safely removed to air.

In support of the hypothesis that carbonic oxide is, apart from its influence on hæmoglobin, a physiologically indifferent gas I may quote here the following experiment, made on an animal devoid of hæmoglobin.

Two mixtures are made, the one of 20 volumes of oxygen and 80 of carbonic oxide, the other of 20 volumes of oxygen and 80 of carbonic acid. Into each of these mixtures a cockroach (Blatta orientalis) is brought. In the carbonic oxide mixture the animal is not sensibly affected, even after a week[1]. In the carbonic acid mixture, on the other hand, a cockroach almost instantly exhibits convulsive movements, and

[1] In one experiment a cockroach was kept without injury in a carbonic oxide mixture for 18 days. At the end of this time the residual atmosphere had the following composition:

Carbonic oxide	71·41
Oxygen	14·21
Nitrogen	9·34
Carbonic acid	5·04
	100·00

becomes quite motionless at the end of from 20 to 30 seconds[1]. It appears to be dead, but nevertheless recovers after a time if taken out before too long. This experiment shows in a striking way the contrast between the essentially indifferent gas, carbonic oxide, and the essentially poisonous gas, carbonic acid.

It is now necessary to discuss more in detail the probability of the hypothesis advanced above that the abolition of the poisonous action of carbonic oxide when the oxygen tension is raised to two atmospheres is due to the fact that the animal can live on the oxygen simply dissolved in the blood.

In the absence of directly obtained data as to the coefficient of absorption of oxygen in blood we may provisionally take as a basis for calculation the number ·0262, given by Zuntz[2] as probable from the results of experiments by Paul Bert on the solubility of nitrogen in blood. Arterial blood contains usually about 20 % of its volume of oxygen, combined in the red corpuscles. Of this oxygen about six or eight volumes are, under ordinary circumstances, used up in the circulation, so that six or eight volumes of oxygen would appear to be necessary to supply the normal requirements of the tissues. Now on the above assumption blood will retain in simple solution about 2·6 % of its volume of oxygen in presence of an atmosphere of pure oxygen, or about 0·5 % in presence of air. At two atmospheres of oxygen blood will dissolve 5·2 % of oxygen. This dissolved oxygen will, moreover, probably be particularly easily available for the wants of the tissues, since its tension is very high, and it will therefore probably pass very easily and completely through the capillary walls.

Now 5·2 volumes per cent. of oxygen will be scarcely as much as is required by the animal. Nevertheless the latter possesses an easy means of making this reduced quantity suffice—namely by increasing the rate of the circulation. During any serious exertion the respiratory exchange of such animals as have been investigated is enormously increased—often to about ten times the normal value, or probably more. To cover this increase the rate of circulation must apparently be also very largely increased, probably by several times. Even were the whole of the oxygen of the arterial blood used up the quantity would not be anything like sufficient to supply the needs of the tissues during exertion, unless the rate of circulation were largely increased.

[1] An almost equally rapid effect is produced by putting the animal in pure hydrogen, and thus depriving it of oxygen.

[2] *Hermann's Handbuch*, IV. 2, p. 16.

If then the rate of circulation were similarly increased in an animal deprived of the use of its red corpuscles, but breathing in an atmosphere of oxygen at double the normal pressure, the requirements of the tissues for oxygen could easily be covered. It is also possible to see how, as in the last experiment on page 213, an animal might still live for a short time when deprived of the use of its corpuscles in an atmosphere at ordinary pressure consisting of two parts of oxygen and one of carbonic oxide.

There can be little doubt that with high carbonic oxide tensions, such as those employed in the pressure experiments just described, the corpuscles are practically saturated with carbonic oxide, and so put completely out of action[1]. Both theoretical considerations, and the examination of the blood of various animals which have died on lowering the pressure, confirm this assumption. In a future paper I hope, however, to communicate more direct evidence on this and a number of further points connected with, and suggested by, the action of carbonic oxide on mice and other animals, including man.

The theory advanced seems to explain completely both the abolition, at high oxygen tensions, of the poisonous action, and the effect of simultaneously diminishing the oxygen and carbonic oxide tension. As might be expected the effect of simultaneous diminution is most striking with high initial oxygen tensions. With initial tensions of less than an atmosphere the oxygen simply dissolved in the blood is of less relative importance to the animal, so that the symptoms come to depend chiefly on the relative affinities for hæmoglobin of the two gases, and the effect on the animal of simultaneous proportional diminution of their tensions is less marked, as in the experiment described on page 209. Finally, the theory explains the fact that the slight effects produced by carbonic oxide even in presence of oxygen at two atmospheres of pressure do not increase on raising the carbonic oxide tension above about 10 % of an atmosphere.

[1] It might be thought that possibly the relative affinities of oxygen and carbonic oxide for hæmoglobin are different at high pressures from what they are at low pressures, and that consequently the corpuscles are not saturated with carbonic oxide at the pressure employed in these experiments. To test this hypothesis I put a dilute solution of blood in the pressure apparatus, with a pressure of two atmospheres of oxygen, and observed its changes of colour on letting in carbonic oxide. But even with a tension of as little as 10 % of an atmosphere of carbonic oxide the solution gave on shaking the same tint as part of the same solution saturated with carbonic oxide. The saturation of the blood was thus practically complete at this tension, in spite of the high oxygen pressure.

Chief Conclusions.

1. The poisonous action of carbonic oxide diminishes as the oxygen tension increases, and *vice versâ*. At a tension of two atmospheres of oxygen this poisonous action is abolished in the case of mice.

2. The disappearance of the poisonous action is due to the fact that at high oxygen tensions the animals can dispense entirely with the oxygen-carrying function of hæmoglobin.

3. The poisonous action of carbonic oxide is entirely due to its power of combining with the hæmoglobin of the red corpuscles, and so putting them out of action as oxygen-carriers.

ABSTRACT

Hunt, T. K., B. Zederfeldt, and T. K. Goldstick.

Oxygen and healing.

Am. J. Surg. 118:521-526, 1969.

Oxygen is essential to metabolism in the wound for (1) energy production, (2) collagen synthesis, and (3) cell proliferation. Oxygen may be necessary in other ways, but if so, the other mechanisms are unknown.

Measurements of oxygen tension of wound fluid and of oxygen gradients across the wound edge lead to the tentative conclusion that most wounds heal in an environment which is poor in oxygen. The rate of wound healing, therefore, may be limited by the oxygen supply. This implies that under some conditions, wound healing may be improved by the addition of oxygen. There is some support in the literature for this concept. Oxygen transport to tissue is easily decreased by a variety of physiologic conditions. At the present state of our knowledge, it appears particularly important for the surgeon to provide adequate wound oxygenation by maintaining blood volume and insuring that all factors influencing tissue perfusion are optimally supported.

Reprinted from TRANSACTIONS & STUDIES OF THE COLLEGE OF PHYSICIANS OF PHILADELPHIA
4 Ser., Vol. 33, No. 1, July, 1965
Printed in U.S.A.

Medical Implications of High Oxygen Pressures[1]

By CHRISTIAN J. LAMBERTSEN, M.D.[2]

THE rational use of high oxygen pressures in medicine is related to a simple but fundamental physical study performed by a Fellow in another distinguished College. William Henry reported his findings in the Philosophical Transactions of the Royal Society of London, 1803, relating gas pressure and the solubility of gases in water, as follows: "But, as the spaces occupied by every gas are inversely as the compressing force, it follows, *that water takes up, of gas condensed by one, two, or more additional atmospheres, a quantity which ordinarily compressed, would be equal to twice, thrice, &c. the volume absorbed under the common pressure of the atmosphere.*" This statement, now well known as Henry's Law, means that by administration of oxygen in a compression chamber it is possible to drive large amounts of oxygen into physical solution in the arterial blood. One result of improved arterial oxygen content, even without improvement in cardiac function, is an increase in what can be considered "cardiac oxygen output" and "tissue oxygen flow".

An equally important consequence of exposure of the blood to high oxygen pressure in the lungs is the increased oxygen partial pressure in the arterial blood flowing into the tissues, which provides a greater pressure head for diffusion of oxygen from the capillary to the metabolizing cell. These two related forms of improved arterial oxygenation are important in conventional inhalational therapy at one atmosphere. Examples of conditions in which an increase of inspired oxygen pressure to several atmospheres may provide still further therapeutic gains are shown in Figure 1. In most of the examples cited the practical utility of high oxygen pressures has been inadequately appraised.

In many clinical states, death of the cell or death of the individual is due to an inadequacy of oxygenation. Figure 1 emphasizes conditions in which gains may be proportional to the degree of hyperoxygenation. Purposely omitted from the figure are situations such as narcotic or other respiratory depressions, where the lungs and circulation are competent and hypoxia is readily overcome by oxygen administration at one atmosphere in a hospital room.

Treatment of disease by exposing patients to an environment of compressed air, but not to pure oxygen, was carried out by physicians in several countries during the 19th century (32). These included men of stature such as

[1] Alvarenga Lecture XXIV, The College of Physicians of Philadelphia, 2 December 1964.

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MEDICAL IMPLICATIONS OF HIGH OXYGEN PRESSURES

DEFECTIVE PULMONARY O_2 UPTAKE	PULMONARY EDEMA HYALINE DISEASE ATELECTASIS
DEFECT IN O_2 TRANSPORT BY BLOOD	CARBON MONOXIDE POISONING METHEMOGLOBINEMIA SEVERE HEMORRHAGE
DEFECT IN TISSUE BLOOD FLOW	CORONARY OCCLUSION
	THROMBOSIS, THROMBOEMBOLISM < MESENTERIC, PERIPHERAL ART, PULMONARY
	AEROEMBOLISM AND BENDS
RADIATION THERAPY OF NEOPLASMS	
ANAEROBIC INFECTIONS	GAS GANGRENE TETANUS
SURGICAL PROCEDURES	PLASTIC SURGERY CARDIOVASCULAR SURGERY NEUROSURGERY

FIG. 1.

Forlanini of Italy, who is better known for his contributions to the technique of artificial pneumothorax (24) (Fig. 2). The early employment of air compression chambers, including a pressurized, mobile operating room constructed in 1879 (23), had no clear therapeutic basis. Even as late as 1930, a massive, five-story, 60 room, 64 foot diameter, spherical compressed air chamber in Cleveland, Ohio was used in the scientifically irrational treatment of such disorders as diabetes, syphilis and neoplasms (20) (Fig. 3). The Bureau of Investigation of the American Medical Association was unsuccessful for several years in condemning this "therapy" (11), but eventually it was discontinued. The giant chamber was demolished in 1942 and undoubtedly contributed heavily to the success of rearmament for World War II.

It is evident, then, that pressure therapy is not new. However, except for some very limited explorations by Priestley with Phlogiston, his newly discovered oxygen (41), and the extensive investigational efforts of Paul Bert in the late 1800's (5), medical interest in compressed gases was not truly based on rational concepts of increased oxygenation.

Reason appeared only after therapy by administration of oxygen itself was begun, and reason did not appear all at once. Largely due to the interest and work of Barach (1), the therapeutic use of oxygen at normal atmospheric pressures became widespread prior to World War II. Between 1940 and the present time, physiological studies related to aviation and diving medicine have led to further understanding of the physiological and toxic effects of oxygen. They have also awakened interest in the possible applications of very high oxygen pressures to clinical problems.

Probably the first important medical use of pure oxygen administration at several atmospheres pressure was to speed the elimination of helium after a deep, helium-oxygen dive, and thus minimize the likelihood of decompression sickness (3). Much later, oxygen was administered to schizophrenic patients at four atmospheres absolute pressure in a clinical study of "oxygen convulsions" as a substitute for the standard electroshock procedure (Unpublished observations, Ewing, J. H., Lambertsen, C. J., Freyhan, F. A., Kough, R., Stroud, M. W., and Gould, R.). Next, oxygen at high pressures began to be used as a means of increasing the sensitivity of tumors to therapeutic ionizing radiation (15). Then, in about 1956, the concept of "oxygen drenching" was proposed as a means of prolonging the viability of organs subsequently subjected to circulatory arrest (6). Therapy of the reversible poisoning

FIG. 2. Luxurious compression chamber used by Forlanini in 1875 (24).

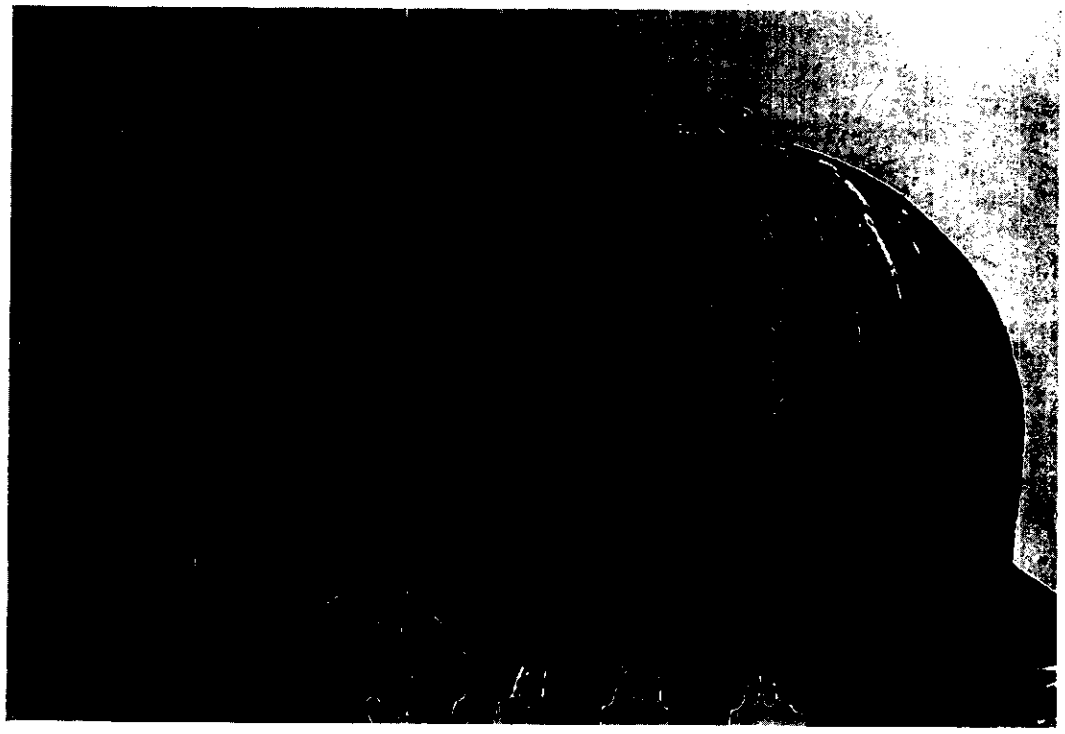

FIG. 3. Giant, multi-roomed pressure sphere built in Cleveland, Ohio and used by Cunningham.

due to specific chemical binding of carbon monoxide to hemoglobin, studied early (28), began to receive renewed attention (22, 40, 44). Eventually, high oxygen pressures were successfully applied to the treatment of Clostridial infections such as gas gangrene (9, 10), and to the relief of bends (47). As is usual when interest outstrips the capacity for obtaining information, the extensive clinical application of high oxygen pressures to medical and surgical problems has temporarily outstripped its evaluation through controlled basic and clinical studies (36). For this reason it is especially important to consider the fundamental effects of hyperoxygenation.

Physiological Basis for Oxygenation At Increased Ambient Pressure

"Oxygen Drenching" and the Duration of Tissue Oxygen Stores

As warm-blooded animals, we are dependent upon a continuing supply of oxygen to the metabolizing tissues. Tissue stores of oxygen in physical solution are normally extremely small and, as shown in Table I, arrest of the circulation should lead to use within about 3 seconds of the minute amount of oxygen stores of brain tissue (25). The result is unconsciousness followed by progressive tissue destruction. The table shows further that administration of pure oxygen at 1.0, 2.0, 3.0 atmospheres and higher pressures will lead to an increase of tissue oxygen stores. However, due to the high rate of normal brain metabolism, any extension of consciousness, cell function and survival following circulatory arrest will be measured in seconds, even at 3.0 atmospheres. Hypothermia will increase this time, but periodic reestablishment of blood flow is necessary for survival.

Factors In Tissue Oxygenation

Whole body oxygenation. The dynamics of normal cellular oxygenation depend not only upon the entering partial pressure of oxygen (Po_2 in mm Hg) and the amount of oxygen flow but also upon the diffusion distance from capillary to cell, the characteristic resistance of the tissue to diffusion, and the rate at which the metabolizing cell is consuming oxygen. The available information concerning the relationships of these factors has been described in several presentations (16, 25).

The overall normal daily oxygen uptake and metabolism (Table II) reflects the amazing capacity of the physiological mechanisms to obtain and deliver oxygen to the cells. In one day a normal individual, pumping nearly 8000 liters of blood, consumes about 368 liters of oxygen from the much larger amount which is circulated through his tissues. The digestive system requires the greatest amount of this, but the needs of the brain are almost as large.

Gas exchange across a tissue vascular bed. The relationships among entering (arterial) oxygen tension, blood flow, metabolism, and blood oxygen transport are shown diagrammatically in Figure 4. The figure is designed to show the average of the events in all the capillaries in an organ such as the brain. An arterial, a capillary and a venous section are shown; the capillary section represents both

TABLE 1

THE QUESTION OF OXYGEN "DRENCHING" AND ISCHEMIC TISSUE SURVIVAL

GAS BREATHED	CELL O_2 STORES (Estimated Mean)	DURATION OF CONSCIOUSNESS * ON VENTRICULAR ARREST	RATE OF CELL DEATH
AIR, 1 ATM.	0.2 cc/100 Gm	3 seconds	?
O_2, 1 ATM.	0.4 cc/100 Gm	6 seconds	?
O_2, 2 ATM.	1.1 cc/100 Gm	15 seconds	?
O_2, 3 ATM.	1.9 cc/100 Gm	29 seconds	?

*Estimated at normal brain O_2 consumption of 3.5 cc O_2/100 Gm brain tissue per minute, cell oxygen stores exclusive of capillary hemoglobin.

TABLE 2

24 HOUR LOGISTICS OF OXYGEN

STRUCTURE	MASS KG.	O_2 CONSUMED PER DAY L.	BLOOD FLOW PER DAY L.
WHOLE BODY	63	368	7,800
DIGESTIVE ORGANS	2.6	73	2,160
KIDNEY	.3	25	1,814
SKELETAL MUSCLE	31	71	1,205
BRAIN	1.4	67	1,080
SKIN	3.6	17	663
HEART	.3	42	324
RESIDUAL	24	72	547

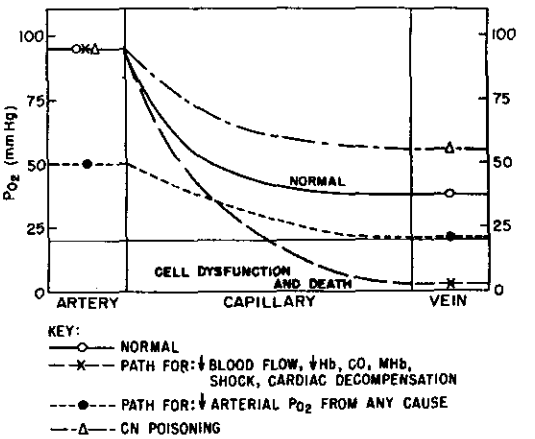

FIG. 4. Tissue capillary gas exchange.

the length of the capillary and the time of blood passage through the capillary bed. The measured values shown are those for normal (resting, air-breathing) arterial and internal jugular venous blood. From these and values for blood oxygen capacity, the rate of fall in P_{O_2} along the capillary has been calculated on the assumption that the rate of oxygen loss to the tissue is uniform. The figure emphasizes that, even with a normal entering arterial P_{O_2}, severe and damaging cellular anoxia can result from any of several disorders which reduce the rate of oxygen flow through the capillary. However, in tissues poisoned by cyanide, oxygen metabolism will be suppressed and failure of intracellular oxidations will occur in the presence of *greater* than normal oxygenation. Finally, if blood flow and oxygen carrying capacity are sustained, a state of lowered arterial P_{O_2} may still provide sufficient oxygen to prevent damaging cellular anoxia.

The fall in P_{O_2} from red cell to mitochondrion. Figure 4 emphasizes several types of alterations in the capillary P_{O_2} which are important primarily because they influence delivery of oxygen to points of oxidative activity within the metabolizing cell. Figure 5, constructed from indirect measurements summarized elsewhere (25), illustrates reasonable values for diffusion distance from a capillary and for the fall in oxygen pressure from the indicated mean capillary oxygen tensions. Note that these estimates suggest a gradient of about 2 mm Hg from hemoglobin molecule to the capillary wall, and up to as much as 25 mm Hg to a distant cell. A gradient of only 1 mm Hg suffices to transfer oxygen across the cell itself and about 0.1 mm Hg permits diffusion within the mitochondrion where the essential oxidative processes occur (25).

THE EFFECTS OF HIGH OXYGEN PRESSURES UPON OXYGENATION OF BLOOD AND TISSUES

During air breathing at sea level, arterial hemoglobin saturation is normally close to 100 percent (about 97–98% saturated) (37). For this reason, oxygen administration at any pressure to individuals with normal arterial oxygenation can produce only a slight, and therapeutically insignificant, increase in chemically bound oxygen. However, the increase in physically dissolved oxygen produced by oxygen administration (about 2.14 ml O_2/100 ml of blood per atmosphere) is extremely important. At an inspired oxygen pressure of three atmospheres, for example, over six ml of additional oxygen is driven into physical solution in the water of the blood. Figure 6 shows the addition of this physically dissolved oxygen as a slight, linear rise of the lower oxygen uptake curve. In the upper curve which depicts the characteristics of hemoglobin oxygen uptake and release in the normal state at sea level, A and V represent average values for arterial and mixed venous oxygenation. The fall in P_{O_2} across the tissue capillary bed during air breathing is seen to be close to 50 mm Hg. When oxygen is breathed at three

atmospheres, the removal of physically dissolved oxygen from the blood in the tissue capillaries leads to an extreme fall in oxygen tension, as great as several thousand mm Hg. Thus, at three atmospheres in an actively metabolizing organ like the brain, the tissue oxygen requirement is so great that the oxygen pressure of blood is lowered until, after most of the physically dissolved oxygen has been used, some of the oxygen held by hemoglobin is released.

If the partial pressure of oxygen in the arterial blood is sufficiently elevated, it should be possible to supply the oxygen needs of the tissues entirely by oxygen in physical solution. This condition has been approached in animals severely poisoned by carbon monoxide (28), in an animal whose blood was almost completely replaced by hemoglobin free solutions (7), and in men exposed to pure oxygen at 3.5 to 4.0 atmospheres pressure (34).

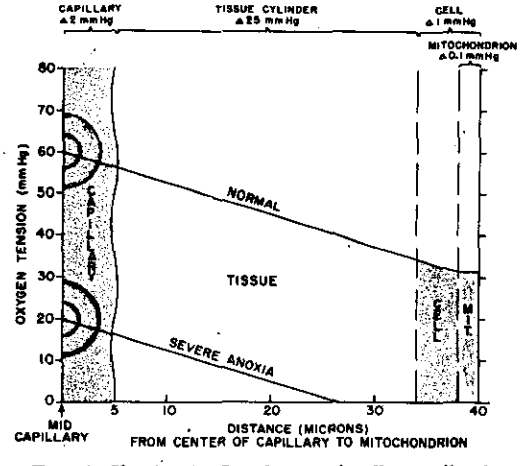

FIG. 5. The fall in P_{O_2} from red cell to cell mitochondrion.

It is important to realize that in normal individuals, even three atmospheres of inspired oxygen will not provide extreme and equal elevation of P_{O_2} in all tissues. Table III and Figure 7 are based upon average normal values for organ blood flow and metabolism and upon the influence of inspired oxygen pressure upon arterial oxygen content; they provide estimates of the rises in venous oxygenation expected from oxygen administration to normal subjects at three atmospheres pressure (34). Clearly, the "dose" of oxygen should not be expected to be the same for each tissue. An organ such as the kidney, which has a blood flow disproportionately high even for its active metabolism, may be exposed to a greater mean tension of oxygen than the liver or the constantly exercising heart. In Table III the only actual measurements for high oxygen effect upon organ venous blood are those for the brain; the other values were calculated to emphasize the order of magnitude of oxygen effects to be expected. Certainly to completely supply oxygen to all cells by way of physical

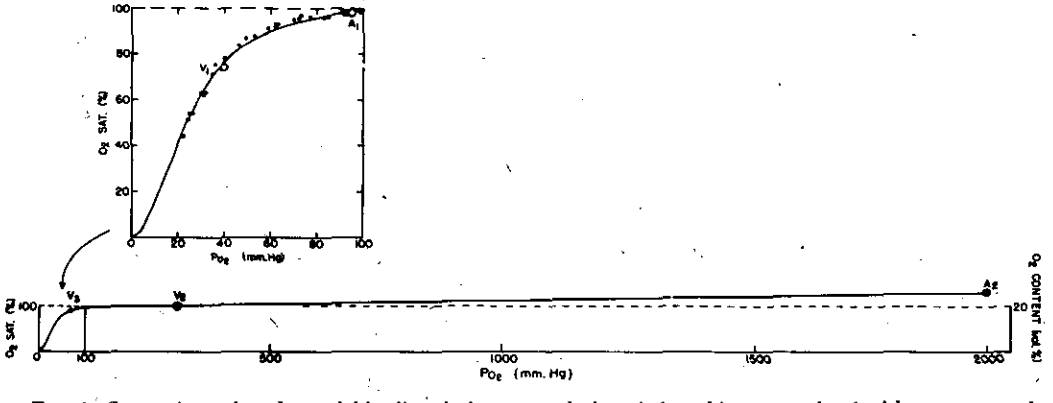

FIG. 6. Comparison of oxyhemoglobin dissociation curve during air breathing at sea level with oxygen uptake curve breathing oxygen at 3.5 atmospheres. The slope of the oxygen uptake curve above complete saturaton of hemoglobin represents the physical solution of oxygen in the water of blood (From Lambertsen, C. J., *Handbook of Physiology* (34)).

TABLE 3

EFFECT OF O_2 AT 3.0 ATM. ON OXYGENATION

ORGAN OR TISSUE	BLOOD FLOW ml/100G/min	O_2 USE ml/100G/min	$A\bar{V}O_2$ ml/100ml	AIR BREATHING VENOUS P_{O_2} mm Hg	OXYGEN BREATHING VENOUS P_{O_2} mm Hg
HEART	84	9.7	11.4	21	**40**
BRAIN	54	3.3	6.2	35	**50**
MUSCLE	3	0.16	6.0	36	**300**
HEPATIC-PORTAL	58	1.96	3.4	46	**900**
SKIN	13	.33	2.5	52	**1190**
KIDNEY	420	6.0	1.4	63	**1543**
CAROTID BODY	2000	9.0	.15	100	**1900**

solution it will be necessary to grossly raise inspired P_{O_2} above three atmospheres, to reduce tissue metabolism by anesthetics or hypothermia, or to increase the blood flow in the tissues (34).

The combination of hypothermia and hyperoxygenation deserves continued attention. The physical solubility of oxygen in body fluids increases as body temperature is lowered. This is relatively unimportant during air breathing at sea level. However, as inspired oxygen pressure is raised, e.g. to two or three atmospheres (Figure 8), marked improvement in oxygen transport is produced by tolerable hypothermia. When to these factors are added the suppression of metabolic demand for oxygen and the probable increase in tolerance to oxygen poisoning during hypothermia, it becomes likely that the combination of the two measures may provide for more than additive benefits (34).

The extreme effect and the importance of alternations in blood flow through an organ during hyperbaric oxygenation is evident in Figure 9, which summarizes the results of many experiments in normal men (34). The illustrated path of fall in mean oxygen pressure across the capillary bed is calculated (38) from measurements of arterial and internal jugular venous oxygen tension. Since oxygen administration leads to a moderate cerebral vasoconstriction in normal men, as mentioned

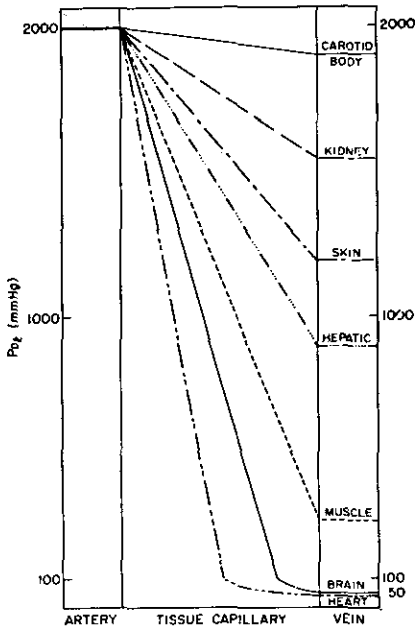

FIG. 7. The influence of high oxygen pressure on organ oxygenation.

above, even 3.5 atmospheres of inspired P_{O_2} does not prevent the use of some oxygen from hemoglobin. However, when brain vessels are dilated by administering carbon dioxide with the oxygen (upper curve), an approximately 1000 mm Hg rise in brain venous P_{O_2} occurs (38).

Carbon dioxide transport function is also modified by hyperoxygenation. The prevention

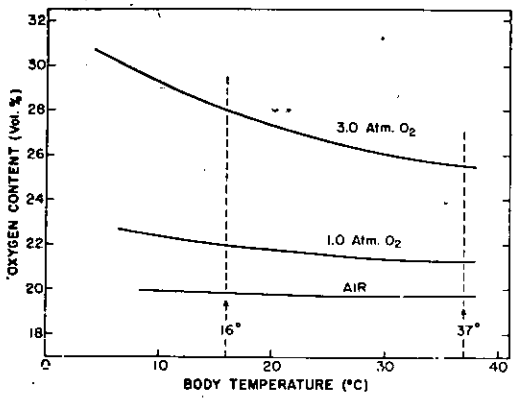

FIG. 8. The effect of hypothermia and oxygen administration on blood oxygenation.

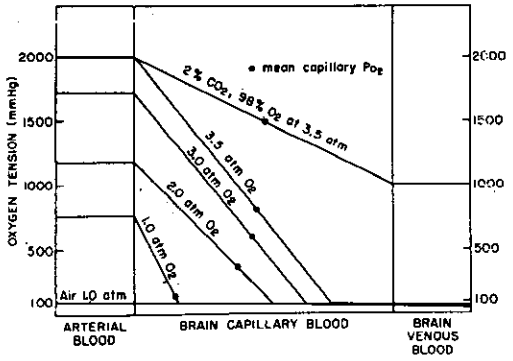

FIG. 9. Diagram of changes in blood P_{O_2} during passage of blood through brain capillary in man, based upon measurements of arterial and internal jugular venous blood.

of hemoglobin reduction interferes with the release of base which normally aids in the buffering of carbon dioxide. The result is a definite rise in tissue P_{CO_2}, which in the brain is self-limited to about five mm Hg (34). This rise in tissue acidity has considerable physiological interest but should not, as in the past, be thought to produce the toxic effects of oxygen breathing.

Acute Physiological Effects of Oxygen

This lecture, with its emphasis upon the therapeutic aspects of hyperbaric oxygenation, does not allow full consideration of the harmless and reversible actions of oxygen upon normal processes. Figure 10 summarizes only a few of the effects of oxygen observed in normal men and animals. These physiological effects include not only the alterations of oxygen and carbon dioxide transport already considered, but also a concurrently stimulant and depressant effect upon respiration, constriction of cerebral, retinal and renal vessels, suppression of the normal chemoreflex response to carbon dioxide administration, and diminution of sympathetic tone. The figure shows that following oxygen administration a number of adjustments are made which result in the establishment of a series of new equilibrium states (34). The actions of oxygen, of interest in their own right, have additional importance as potential modifiers of the responses to drugs used as adjuncts in pressure therapy.

Hyperbaric Oxygenation In Specific Medical Conditions

Although the use of oxygen at one atmosphere is not yet being fully exploited in medicine, several clinical situations are now receiving considerable attention as subjects for study of oxygen therapy at several atmospheres pressure. The most important of these are as follows:

Bends and air embolism. These are quite different conditions. In air embolism air enters the circulation from an external source such as an overdistended lung, or during cardiovascular surgery or a neurosurgical procedure. In bends the nitrogen dissolved in tissues during an exposure to increased pressure forms bubbles in the tissues when the pressure is lowered too rapidly to permit normal elimination of nitrogen via the circulation and lungs.

The problem in both bends and air embolism is to dissolve the circulation-obstructing and tissue-distorting bubbles so that the nitrogen can be harmlessly transported to the lungs as a gas in solution. The classical Navy treatment of bends, recompression with air to six atmospheres to reduce the bubble to about one-sixth its size, is effective. However, resolution of the compressed bubbles is very slow, since the compressed air breathed itself contains nitrogen

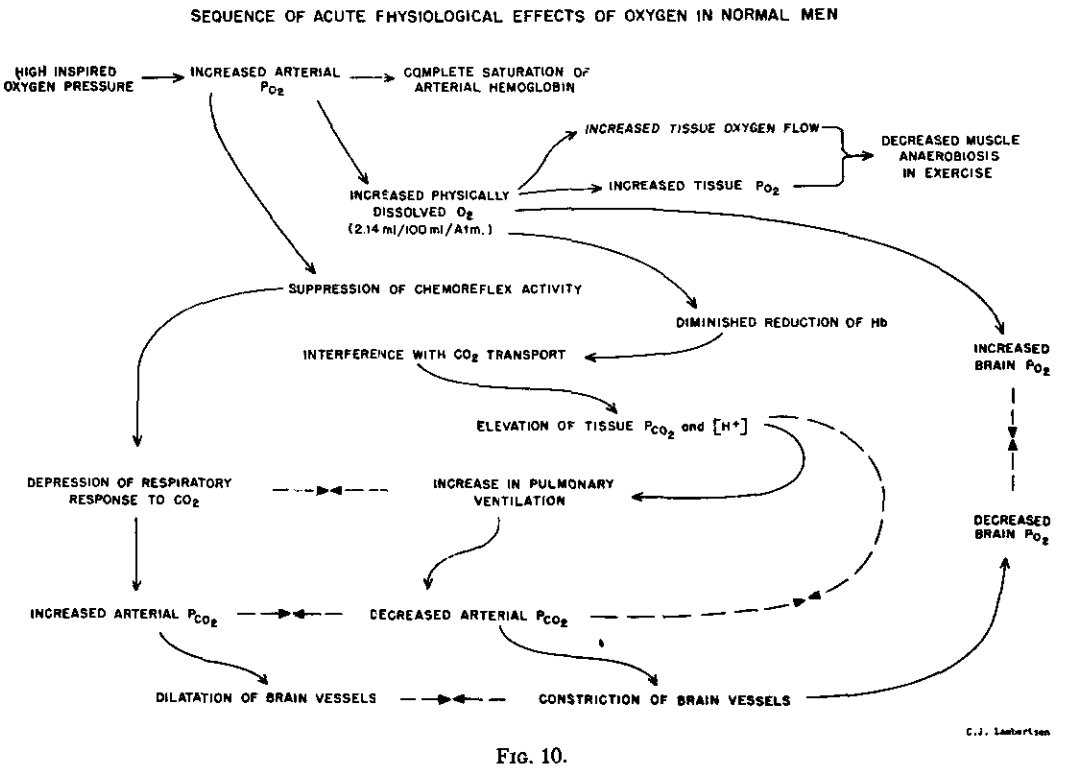

FIG. 10.

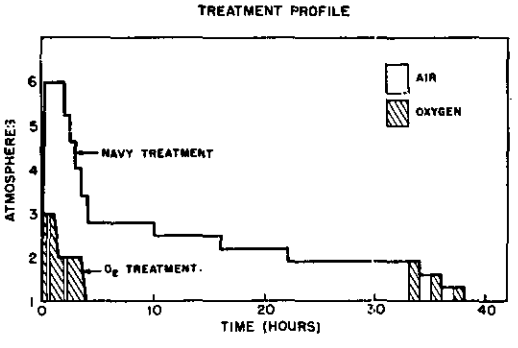

FIG. 11. Comparison of classical U. S. Navy treatment of bends employing compressed air at 6 atms. with newly developed U. S. Navy oxygen method for treatment of bends.

at high pressure and leads to maintenance of a high P_{N_2} in the blood and tissues. The uptake of nitrogen during treatment periods of as long as 48 hours often leads to additional severe bends in the patient or in his physician attendants when decompression is ultimately performed.

Development of the use of pure oxygen at high pressure to treat severe bends and air embolism has drastically reduced the time, the pressure and the equipment required to treat bends (47). Figure 11 compares the treatment profile using oxygen with the classical air method. The use of oxygen at pressures up to 3 atmospheres depends only in part upon the reduction of bubble size by compression itself. Important additional gains are accomplished by a) the rapid *rate of decrease* in bubble size due to the establishment of a maximal outward gradient for nitrogen, and b) establishment of a high gradient of oxygen tension to the regions of impaired circulation. Measures for treating bends were once important only to the diver and caisson worker. If high pressure chambers become extensively used in medicine, oxygen therapy will be required to treat bends generated in the physician as well.

Carbon monoxide poisoning. There is a rational indication for therapy with oxygen at high pressure (22, 40, 44). When our chamber

became available for pressure work in 1947 I arranged with the Director of nearby Philadelphia General Hospital to treat what I expected would be the large number of cases of carbon monoxide poisoning occurring annually in Philadelphia. I learned that severe CO poisoning was extremely rare here, and, as CO itself was eliminated from the household gas system by conversion to natural gas, the number of cases became even fewer and no opportunities presented themselves. However, high pressure oxygen treatment of carbon monoxide poisoning is now extensively used in Scotland (44), where open coal fires and poor ventilation predispose to the intoxication.

Figure 12 shows, for animals exposed to carbon monoxide, the rate of decrease in carboxyhemoglobin saturation during air breathing, its acceleration by oxygen administration at one atmosphere, and the still faster rate of elimination of CO at 2.5 atmospheres (40). This accelerated CO elimination is a result of a dynamic chemical competition of oxygen and CO for hemoglobin. In addition, hyperoxygenation results in an increased pressure head (P_{O_2}) and an increase in tissue oxygen supply in the form of physically dissolved oxygen. At a high enough inspired oxygen pressure (and for a period of time limited in duration by oxygen poisoning) survival should occur even if all hemoglobin molecules are occupied by carbon monoxide.

Radiation therapy of neoplasms. The radiation

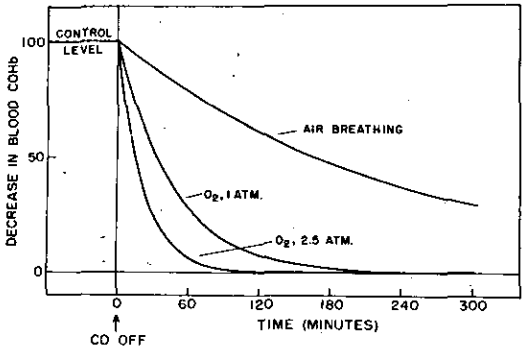

FIG. 12. The effect of increased P_{O_2} on carbon monoxide elimination in men. (Data from Pace, *et al.* (40).)

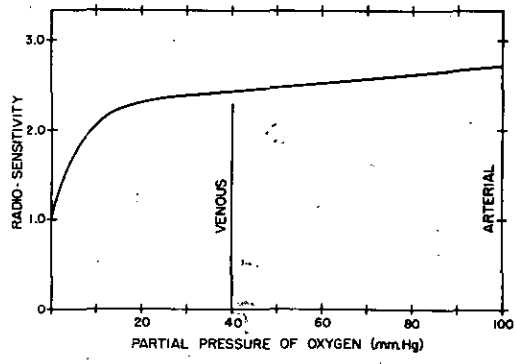

FIG. 13. Alteration of radiosensitivity of plant and animal tissue by change in cellular P_{O_2}. (After Gray (27)).

treatment of certain tumors such as bronchogenic carcinoma has been carried out in patients breathing oxygen at three atmospheres pressure (14, 15). Figure 13 shows the primary basis for combining oxygen and radiation as therapeutic measures. It represents the in vitro sensitivity of various cell types, including yeast, bacteria, plant and animal tumor cells, at different levels of environmental oxygen tension. The figure indicates that sensitivity to ionizing radiation is much reduced at very low oxygen pressures (27). It has been proposed that, as certain tumors outgrow their blood supply, the cells which are most distant from the capillaries become anoxic in vivo and thus resist destruction by radiation at doses which will damage both well oxygenated tumor cells and surrounding normal tissue (14, 15, 27). To restore the relatively anoxic tumor cells to normal radiosensitivity, the patient is exposed to a high oxygen pressure. Under this condition of high pressure oxygenation, radiotherapy is carried out. For the oxygenation of a poorly perfused tissue to be appreciably improved, very high inspired oxygen pressures of at least three or four atmospheres must be used. It should also be noted that the effect of improved oxygenation tends to be limited as oxygen pressure is progressively increased.

High oxygen pressures in coronary disease. Whether hyperbaric oxygenation will find a place in the treatment of acute coronary occlusion in man is now highly uncertain. The

effects of oxygen at one atmosphere in this condition are at last being studied exhaustively (39). Some, but not all, studies in animals indicate that higher than atmospheric pressures provide a significant degree of protection against experimentally induced coronary embolization or ligation (13, 31, 33). However, increased survival was found only when embolization was induced *while* the animal was breathing oxygen at high pressure (33). Thus far no study in man has demonstrated a significant advantage of hyperbaric oxygen therapy in coronary occlusion (48). Oxygen does relieve the pain of myocardial infarction (8) and elevates oxygen tension at the periphery of induced infarcts (43). Coronary occlusion thus remains a defect in tissue oxygenation and means of increasing the known benefits of oxygen administration at sea level should be carefully pursued. Certainly other factors besides oxygenation are involved in a myocardial vascular occlusion. Nutrient, ionic and membranal factors may remain distorted even if oxygenation itself is somewhat improved. The normal heart, an exercising muscle, has its venous oxygen levels only slightly elevated even during exposure to three atmospheres of oxygen pressure. In a region of occluded circulation still less effect should be demonstrable. Prominent handicaps to study and therapy will continue to be the limitations of pressure and duration of continuous exposure imposed by the pulmonary toxicity of oxygen. If gains are made, they will likely result from repeated, programmed, intermittent oxygen exposures at pressures only slightly in excess of one atmosphere, rather than from infrequent, brief, and abortive exposure to extremely high oxygen pressures.

Anaerobic infections. One of the most clearcut indications for high pressure oxygen therapy appears to be in the treatment of gas gangrene (9, 10). Table IV summarizes a number of important features of this fulminating and necrotizing infection. The organism predominantly responsible for necrotizing myositis is *Clostridium perfringens* (Welchii). It is a common part of our environmental flora and

TABLE 4

ANAEROBIC INFECTIONS

GAS GANGRENE
- Three species of Clostridia produce most of the clinical infections.
  Cl. Perfringens (70%), Cl. Novyi (20-30%), Cl. Septicum (5-10%)
- Normal flora of man and his environment.
- Disease due to opportunity, not increase in virulence.
- Damage is caused by alpha-toxin, a lecithinase, necrotizing, hemolytic, lethal. Fixed in tissues. Fulminating tissue destruction. Toxemia.
- Septicemia results in toxin effects in blood. Hemolysis, renal shut-down.

ANAEROBIC CELLULITIS
- Not necrotizing.

TETANUS
- Fixation of toxin.

becomes dangerous, not through the emergence of especially virulent strains, but when the presence of necrotic tissue and ischemia complicate wound contamination.

Oxygen is an "antibiotic" agent for the anaerobic Clostridial organisms. Exposure of cultures of *Cl. perfringens* to very high oxygen pressures inhibits multiplication of the organisms and can cause their death (9). However, the advantage of high oxygen pressures in the therapy of gas gangrene appears to depend more upon inhibiting formation of the α-toxin, a lecithinase which produces the necrotizing myositis, than upon killing the organisms (9). The toxin apparently is promptly fixed by the local tissues after formation and is not responsible for the severe toxemia of gas gangrene; the decrease in fever and toxemia during oxygen therapy is possibly related to a lessened rate of muscle destruction.

Oxygen administration, even at several atmospheres pressure, cannot be expected to raise cellular oxygen tension or to affect the gas bacillus in regions where the local circulation is not competent. For this obvious reason high oxygen pressure should not be considered a substitute for proper surgical measures including drainage, debridement and amputation. Oxygen, like antibiotic treatment, is only an adjunct to other therapy, but it appears to be an effective and important adjunct. Ways of improving its effect in the necrotizing myositis which is gas gangrene deserves intensive study, as does its possible

role in the less serious forms of anaerobic cellulitis. Thus far there is no clear indication that therapy with high oxygen pressures has a specific effect upon the course of clinical tetanus infections (9, 10).

Other applications. The foregoing are cited as examples of conditions in which high oxygen pressures have been employed in study or treatment. In surgery high oxygen pressures have been employed, with and without hypothermia, to sustain infant or adult patients during repair of cardiac defects (4, 6). Other situations deserving special mention include the general circulatory failure of traumatic shock (18), the decompression, oxygenation and de-gassing of a paralyzed bowel (19), and the treatment of the damaged tissue underlying severe burns. In each of these conditions, the practical application of the evident theoretical advantages of improved tissue oxygenation is distinctly handicapped by the serious problem of oxygen toxicity, which must now be considered.

Oxygen Toxicity

The limits of exposure imposed by oxygen poisoning make it necessary to employ hyperbaric oxygenation on a discontinuous basis. The rate of development of the unfortunate toxicity of a life-sustaining agent, as well as the form it takes, is a function of both the oxygen pressure and the duration of exposure (2).

Pulmonary oxygen poisoning. Two manifestations of oxygen toxicity have particular clinical importance. One is the damage to the respiratory membranes, from nasopharynx to alveoli, which occurs at levels of inspired P_{O_2} too low to produce other demonstrable forms of toxicity (2, 34). This is not surprising since the respiratory epithelium is exposed to a much higher oxygen dose than are the other tissues.

At one third of an atmosphere, equivalent to the 5 psi pressure in the Mercury and Gemini space capsules, it appears that pure oxygen can be breathed for at least a month, or almost indefinitely, without toxic effects (34, 42). In the sea level environment of a hospital, 50 percent oxygen produces no symptoms in 24 hours, but about fifteen to twenty-four hours of continuous pure oxygen breathing causes a moderate degree of chemical pulmonary irritation (17) (Fig. 14). As pressure is raised above one atmosphere the rate of onset of toxicity in animals increases rapidly until at five to seven atmospheres its effects become evident within an hour (2, 15). This phenomenon has not yet been studied in man above one atmosphere.

Central nervous system oxygen toxicity. The second well-recognized form of oxygen toxicity

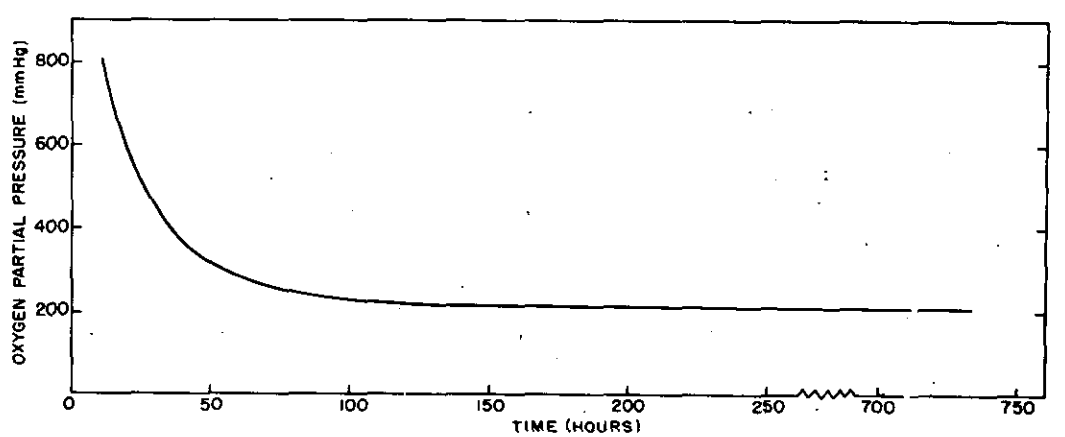

FIG. 14. Tolerance of the lungs to inspired oxygen pressures up to one atmosphere. (After Welch (42, 46)).

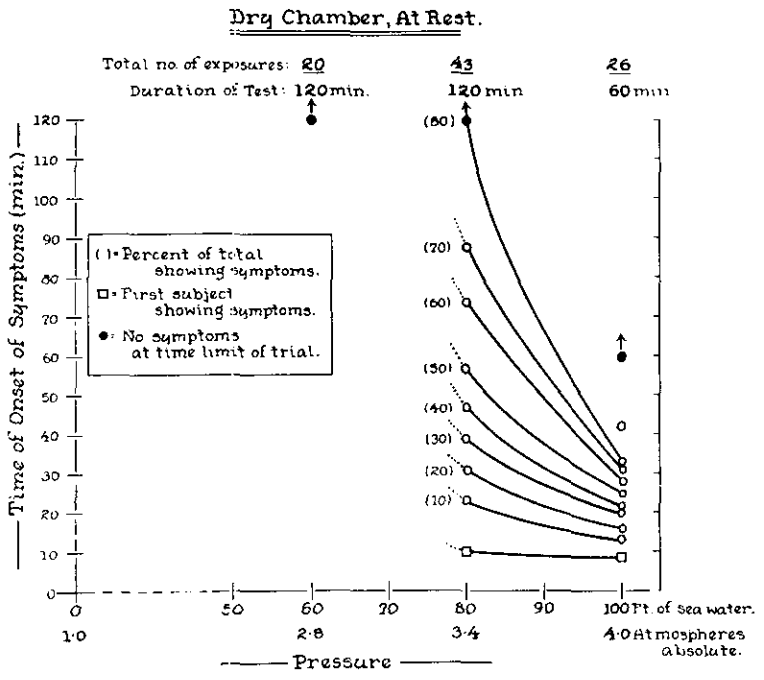

FIG. 15. Tolerance of normal men to pure oxygen at increased ambient pressure. Diagram based upon U.S. Navy studies in World War II (35).

is the generalized, epileptiform, convulsive seizure which results from effects of oxygen upon central neurons (2, 34). At inspired oxygen pressures above three atmospheres, the latent period for development of convulsions in conscious, normal men is shorter than that for production of detectable pulmonary damage, making central nervous system toxicity the limiting factor *in single exposures.* At one atmosphere of inspired oxygen, central nervous system intoxication has not been observed, and pulmonary poisoning limits the duration of exposure. Between these two dose levels, one and three atmospheres, is a region of extreme clinical importance where essentially no information is now available to indicate the duration of tolerance to oxygen of any tissue (34) (Figure 16).

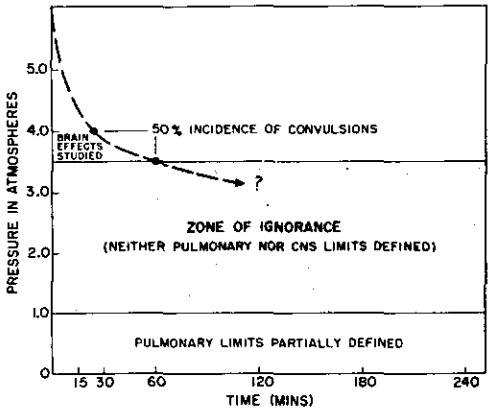

FIG. 16. Tolerance of the brain to high oxygen pressures.

In physically sound men the actual convulsion produced by oxygen is no more dangerous than is an individual epileptic seizure (34). However, the convulsion is a manifestation of the electrical derangements produced by a chemical poisoning. Therefore, if the seizures are ignored or suppressed by drugs such as phenobarbital, it should be recognized that cellular oxygen poisoning will continue and brain damage or death will eventually result (34).

Other forms of oxygen poisoning. As the

effects of oxygen upon man are more extensively studied, evidence of oxygen toxicity may be detected in organs other than the lungs and central nervous system. From evidence of in-vitro studies it is clear that almost any cell, whether plant, animal or microbe, is susceptible to oxygen toxicity and can be expected to be destroyed if the pressure-time dose of oxygen is great enough (16, 26). One unexplained exception to this statement may be the lining cells of the oxygen-secreting swimbladder of deep ocean fish which are exposed to extremely high local oxygen pressures (45).

Due to the great differences in the level of P_{O_2} in various tissues when exposed to a high ambient oxygen pressure (Fig. 7), it is easily conceivable that intolerable oxygen toxicity can be produced in some cells even during failure to relieve anoxia in others (16). For this reason the greatest further gains in application of high oxygen pressures in clinical medicine should come from studies defining and extending the limits of oxygen tolerance.

The biochemical bases for oxygen poisoning. The mechanisms of oxygen poisoning of cell metabolism have been extensively studied for the past twenty years (21, 30). Apparently a high intracellular P_{O_2} can interfere with metabolic processes in several ways. Generally, high oxygen tensions interfere with the oxidation of glucose and with the use of oxygen itself. The effect may well be, at least in part, the result of an excessive rate of oxidation of essential cellular constituents (30). Hyperoxygenation inhibits or inactivates several sulfhydryl containing enzymes concerned with carbohydrate oxidation in the citric acid cycle. It blocks the oxidation of pyruvate and causes its accumulation; this effect may be due to the toxic oxidation of the sulfhydryl-containing substance, CoA. Oxygen also interferes with the formation of high energy phosphate compounds, such as ATP, ADP and AMP, which are important in cell metabolism. In addition to all of the above, high oxygen pressures may inactivate flavine groups of enzymes involved in the electron transport chain (29). With these several sites of oxygen action it is possible that a degree of chemical protection may eventually become feasible. Whether this would aid or negate the beneficial effects of oxygen administration is questionable. At present, prevention of oxygen toxicity at the cell level is no more practical than is the use of drugs to protect against severe radiation damage.

Factors modifying oxygen tolerance. The latent period of central nervous system oxygen poisoning is shortened by muscular exercise and by administration of carbon dioxide during the exposure to high oxygen pressures (2, 34). Drugs which permanently block sulfhydryl enzymes also accelerate the metabolic effects of oxygen toxicity (Haugaard, N., Personal Communication), while sulfhydryl suppliers or protectors of normal sulfhydryl enzymes delay the manifestations of oxygen toxicity (26). The development of oxygen convulsions, but probably not the actual oxygen poisoning, is prevented by barbiturates and other central depressants (21), and should therefore be accelerated by central nervous system stimulants. Cold blooded animals, whose body temperature is kept low, show a much prolonged latent period for oxygen toxicity (2). This and general thermodynamic considerations suggest that in man hypothermia should delay and hyperthermia should accelerate the onset of convulsions.

Intermittent exposure. It has been observed that the rate of recovery from the effects of oxygen toxicity is faster than the rate of development. This finding led to the principle of alternating high and low inspired oxygen pressures to permit greater exposure to increased P_{O_2} within a given period of time without producing oxygen toxicity (35) (Fig. 17). It is hoped that the intermittent, prompt reversal of incipient oxygen poisoning will permit frequent repetition of therapeutic exposures to high oxygen pressure. Although this principle was discovered in man and has been quantitatively demonstrated in animals, the optimal durations of oxygen exposure and interruption of oxygen breathing have not yet been worked out for any pressure in man (34).

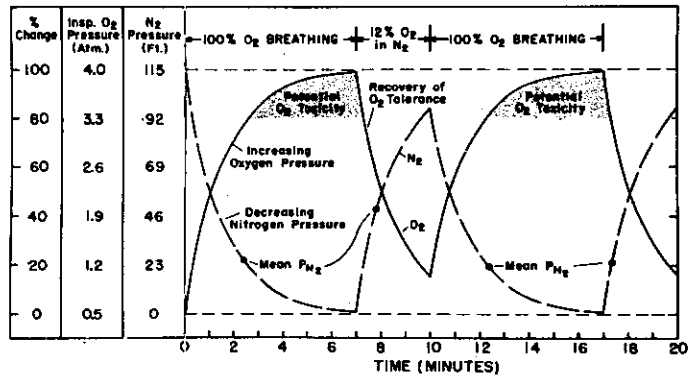

FIG. 17. The use of fluctuating Po_2 in therapy with high oxygen pressures.

PROBLEMS OF DECOMPRESSION AND COMPRESSION

The clinical use of oxygen at pressures above atmospheric pressure involves for the patient and for the attendant many of the same physical and physiological problems faced by the diver. The chamber pressure will ordinarily be increased by compressed *air*, not by oxygen, to avoid what even at one atmosphere would be an extreme risk of explosion or fulminating fire. As the air pressure is raised, the force exerted upon the body surfaces is transmitted uniformly and therefore unperceived throughout all body fluids. Thus, *relative to conditions at sea level*, the pressure of arterial blood in an individual at an ambient pressure of three atmospheres will be over two thousand mm Hg.

Sensations of increasing pressure are normally felt only in the ear, where temporary failure of air to enter the middle ear through the eustachian tube may cause painful inward deformation of the eardrum. Similarly a blocked ostium of a paranasal sinus will result in pain because the increasing absolute pressure in the capillaries and tissues lining the sinus is not balanced by a corresponding increase of air pressure within the blocked sinus. The high pressure gradient from capillary to air space will cause fluid extravasation, capillary rupture and bleeding into the sinus.

At the working pressure, the air breathing attendant may be mildly narcotized by the increased nitrogen tension in his brain. The narcotic effect of nitrogen, barely detectable at three atmospheres, becomes increasingly prominent at higher pressures and can produce unconsciousness at ten atmospheres (12). The oxygen-breathing patient is exposed to oxygen toxicity but, since no nitrogen is accumulated in his tissues during the oxygen administration, he is exposed neither to nitrogen narcosis nor to risk of bends on decompression.

During decompression, gas trapped in body cavities begins to expand, increasing in volume in direct proportion to the decreasing pressure (Fig. 18). The expanding air escapes readily from the middle ear cavity. However, gastrointestinal gas or the air in a pneumothorax at three atmospheres will expand to three times its volume on return to one atmosphere, with potentially disastrous results. Expansion of air trapped in emphysematous bullae may lead to rupture of the bullae and to the development of pneumothorax. Similarly, decompression during breath-holding or with any obstruction to pulmonary ventilation should lead to gross expansion of the intrapulmonic gas, causing rupture of lung tissue and probably massive air embolism.

"Decompression sickness" is a term reserved for the bends. This may occur in individuals who, after breathing air for an extended period of time, decompress too rapidly to allow gradual elimination of the excess nitrogen in the tissues. The rate of nitrogen elimination is circulation-limited and, if rapid return to sea

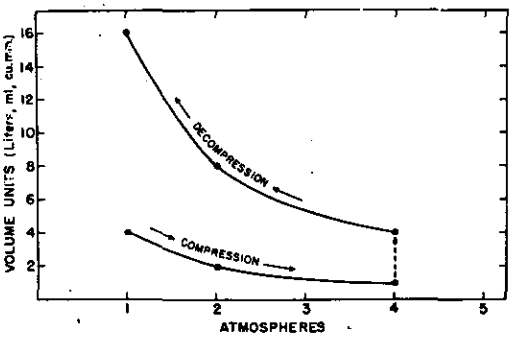

FIG. 18. The effects of pressure changes on gas volumes in body spaces.

level pressure leaves a high partial pressure of nitrogen in a tissue, nitrogen will escape from solution in the tissue fluids to form bubbles. The distortion of tissue and the ischemia produced by the bubbles cause itching, pain, dyspnea or paralysis, depending on whether the bubbles form in the skin, joints, lungs, or central nervous system. Since excess oxygen in the blood is metabolized during one circulation through a tissue, oxygen itself does not produce bends. As pointed out above, if bends due to nitrogen occur in the course of hyperbaric therapy, the most effective treatment is administration of oxygen at increased pressure.

SUMMARY

We have arrived at a reasonable place to end this lecture. It is necessary to sound a strong note of warning that the use of pressure therapy with oxygen is potentially hazardous to patient and physician alike. However, these hazards are subject to logical appraisal in advance and can largely be prevented by awareness of them and by appropriate training of the individuals involved.

Considerable optimism should also be expressed that the use of high oxygen pressures will find a rational and lasting place in therapy. If this prediction is borne out it will be because of meticulous further exploration of the basic effects of high oxygen pressures in normal and pathological states, and on the basis of carefully controlled clinical trials to determine the improvement to be expected with therapy.

In the course of time it is possible that much can be done to extend the therapeutic usefulness of oxygen at high pressures. Of the many avenues which lend themselves to study in man, three appear most deserving of immediate attention. One is the clear definition of the limits of pulmonary oxygen tolerance at rest over a wide range of inspired oxygen pressures. Another is the determination of the most effective schedules for protecting against oxygen toxicity by periodic interruption of exposure to high oxygen pressures. The next is study of the combination of hypothermia and hyperoxygenation for treatment of extreme local hypoxia. Through these and other investigations, opportunity exists for extending not only the practical employment of high oxygen pressures but also understanding of the fundamental principles upon which the ultimately successful therapeutic procedures will be based.

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The Effects of Hyperbaric and Normobaric Oxygen on Cognitive Impairment in the Elderly

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• **Eighty-two elderly subjects with significant cognitive impairment were randomly assigned to treatment with either hyperbaric oxygen, hyperbaric air, normobaric oxygen, or normobaric air. Treatment consisted of two 90-minute sessions a day for 15 consecutive days. Subjects were evaluated on measures of memory and intellectual capacity, as well as on psychiatric symptom rating scales. Results immediately after treatment and at one, two, three, and eight weeks following treatment did not show enhanced cognitive functioning or significantly greater symptom reduction in experimental subjects who received either normobaric or hyperbaric oxygen as compared to controls who received hyperbaric or normobaric air. There was also no evidence of differential treatment effects as a function of initial severity of illness, sex, response to a CO_2 loading test, or presumed evidence of cerebrovascular disease.**

(*Arch Gen Psychiatry* 35:50-56, 1978)

In 1969, Jacobs et al[1] reported improved cognitive functioning in 13 elderly patients with chronic organic brain syndrome following repeated exposure to hyperbaric oxygen. Five control subjects exposed to an air mixture failed to show improvement initially, but did improve later when they were crossed over to oxygen. In the intervening six years, there have been five published reports confirming Jacobs and colleagues' original observation.[2-6] However, only one of these studies utilized a control group. Boyle et al[3] noted significant improvement in memory function in patients receiving a combination of hyperbaric oxygen and 250 mg/day of acetazolamide for ten days. Acetazolamide is a potent carbonic anhydrase inhibitor used mainly as a diuretic. Similar improvement was not observed for the groups receiving either treatment alone or for the control group exposed to an air mixture and given a placebo.

There have also been two studies[7,8] that failed to replicate the original finding by Jacobs et al. The study by Thompson and his associates[8] utilized 21 experimental subjects and four control subjects. These authors failed to note any significant differences between the experimental and control subjects.

As a probable corollary to the finding of the Jacobs' group, two studies have appeared recently on the use of normobaric oxygen for the treatment of psychogeriatric symptoms. An uncontrolled study by Fraiberg[4] reported positive results in disturbed geriatric patients at a nursing center. However, White et al[10] failed to detect any treatment differences between three hospitalized geriatric patients treated with a mixture of 97% oxygen and 3% carbon dioxide and four control patients treated with compressed air.

This brief literature review highlights one of the major problems in evaluating the efficacy of hyperbaric and normobaric oxygen as treatments for cognitive impairment in the elderly, namely, the paucity of studies utilizing control subjects and the small number of control subjects in these studies.

The present collaborative study of the Psychopharmacology Research Branch of the National Institute of Mental Health (NIMH) and the New York University Medical Center was undertaken in direct response to both the importance of the Jacobs et al[1] results and the obvious need for a replication study with enough control subjects to provide an adequate test of the efficacy of hyperbaric and normobaric oxygen.

SUBJECTS AND METHODS

Subjects

Subjects were ambulatory individuals between 60 and 85 years of age who were residing in the community; written consent was obtained from all subjects after the nature of the procedures was fully explained. For admission, they had to attain an age-corrected scaled score of at least 8 on the vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS) as an indication of both adequate premorbid intellectual function and ability to complete the required psychological testing. Subjects were also required to score more than 1 standard deviation below the mean established for their age group and vocabulary level on at least three of five subtests on the Guild Memory Test.[11] This latter criterion was imposed to ensure memory loss significantly greater than that expected in the normal aging process. Subjects with a history of medical problems that would place them at risk on exposure to hyperbaric oxygen were excluded from the study.

The major identifying characteristics of subjects included in the study are outlined in Table 1. The median subject was 72 years of age, had completed high school, and was average in intelligence. There were also approximately equal numbers of men and women. With two exceptions, all subjects received diagnoses of organic brain syndrome (OBS). Circulatory disturbances were cited as the probable cause for the OBS in half the cases and senile brain disease was noted for the other subjects.

For no reason we have been able to discern other than chance, the hyperbaric oxygen subjects were significantly lower in initial full-scale IQ on the WAIS[12] than subjects in the other treatment groups. However, as noted in Table 1, these subjects were not significantly more deteriorated or impaired than those in the other treatment groups.

Table 2 compares subjects in this study with those from other

Accepted for publication May 6, 1977.

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Table 1.—Comparison of Treatment Groups on Identifying Variables

Variable	Normobaric		Hyperbaric		Test Statistic
	Oxygen	Air	Oxygen	Air	
No. of subjects	21	21	20	20	
Age, mean (range)	74 (65-84)	73 (64-85)	71 (64-81)	72 (62-80)	$F = 0.851$ (NS)
Sex, % female	57	57	50	55	$\chi^2 = 0.279$ (NS)
Educational level, median	Attended college	Completed high school	Attended college	Completed high school	...
WAIS full-scale IQ, mean (range)	96 (68-125)	96 (69-128)	90 (64-127)	99 (63-129)	$F = 4.72$*
% Wechsler deterioration	15	15	13	12	$F = .14$ (NS)
Psychiatric diagnosis					
Psychoses associated with cerebral arteriosclerosis†	2	0	0	0	$\chi^2 = 9.507$ (NS)
Nonpsychotic OBS with circulatory disturbance	10	5	7	8	
Nonpsychotic OBS with senile brain disease	9	16	13	12	

*Significant at .01 level (two-tailed).
†When the first two rows in this χ^2 table are combined, the χ^2 is 5.08 with 3 *df*, which is also not statistically significant.

Table 2.—Pretreatment Comparison of Study Subjects With Subjects of Previous Investigations

Investigators	No. of Subjects	Mean Age	Wechsler Memory Quotient
Raskin et al, (current study)	82	72	77
Jacobs et al[1]	18	68	77
Goldfarb et al[2]	16	74	58
Edwards & Hart[3]	20	68	89

Table 3.—Subject Terminations During Acclimation Phase (Days 1 Through 7)

Reason for Termination	Normobaric	Hyperbaric
Unwilling to continue or did not return	7	15
Developed medical problems	3	3
Deteriorating mental condition	0	2
Other	4	4
Total	14	24

studies on mean age and mean Wechsler Memory Quotient. On these variables, our subjects closely paralleled those in the original Jacobs et al[1] study and are clearly less deteriorated than the subjects in the Goldfarb et al[2] study.

Procedure

The study was conducted double-blind, and all subjects meeting the criteria for inclusion were randomly assigned to one of four treatment groups. Twenty-one subjects received normobaric oxygen, 21 normobaric air, 20 hyperbaric oxygen, and 20 hyperbaric air. Subjects who entered the study understood that they would be randomly assigned to one of these four groups and that only one quarter of them would receive hyperbaric oxygen. However, the procedures for administering oxygen or air under the normobaric condition were identical, as were the procedures for administering oxygen and air under the hyperbaric condition. Neither the normobaric nor the hyperbaric subjects were told which treatment, ie, oxygen or air, was being administered. To further maintain the blind condition, six normobaric subjects, three given oxygen and three given air, were run through the study simultaneously in the same hospital room. Similarly, six hyperbaric subjects, three given oxygen and three given air, were run through the study simultaneously in the hyperbaric chamber.

All study personnel responsible for any of the ratings on assessment measures were blind to the treatments assigned to the study subjects. In addition to the study psychiatrist, psychologist, and nurse, this included the psychometrist who administered the psychometric and cognitive tests and the social worker and nurse who obtained information from family informants and from the subjects themselves. Not only were these staff members not told whether the subject was receiving oxygen or air, they were also told not to inquire of either the subject or of other staff members as to whether the subject was assigned to normobaric or hyperbaric treatment. However, this aspect of the double-blind was obviously difficult to maintain, and there were instances where raters did learn that a subject was receiving either hyperbaric or normobaric treatment. There were no instances, however, to our knowledge, where a rater knew that a subject was being given either oxygen or air.

During the first seven days in the study, subjects underwent a series of acclimation trials to the hyperbaric and normobaric procedures. This period was especially critical for subjects who were to undergo hyperbaric treatment, as it provided an opportunity to test their tolerance for increased sustained pressure. From Table 3 we note that 38 subjects who originally started in the study were terminated in the first week and subsequently had to be replaced. An unwillingness to continue or failure to return were the major reasons cited for termination during this phase. It is noteworthy, however, that there were twice as many terminations for these reasons among subjects assigned to the hyperbaric as compared to the normobaric condition. The physical discomfort associated with the increased pressure in the chamber and possibly fear of the chamber itself were judged to be at least partially responsible for the decision of these subjects not to return.

Treatment began on the eighth day in the study and was continued for 15 consecutive days. Both hyperbaric and normobaric subjects were exposed to two 90-minute sessions each day, separated by a three-hour interval. In the hyperbaric condition, experimental subjects breathed pure oxygen at 2.5 atmospheres absolute (ATA) while controls breathed a 10% oxygen, 90% nitrogen gas mixture at 2.3 ATA. Experimental normobaric subjects breathed pure oxygen and normobaric controls breathed compressed air. For both the hyperbaric and normobaric subjects, all gases were administered by full face mask rather than the less efficient aviator mask.

To check on the effectiveness of the gas delivery systems, blood samples were obtained during the first four days of treatment and

Table 4.—Mean Blood Gas Levels

	Normobaric		Hyperbaric	
	Experimental	Control	Experimental	Control
Po_2, mm Hg	391	85	1,128	143
Pco_2, mm Hg	31	35	41	41

Po_2 and Pco_2 levels were calculated. Mean blood gas levels for the four groups during treatment are noted in Table 4. The high Po_2 levels for the hyperbaric and normobaric experimental groups attest to the efficacy of the gas delivery systems.

Evaluations

Two general types of measures were employed to evaluate treatment effects. The first consisted of psychological and psychophysical performance tests designed to assess aspects of cognitive function such as memory, orientation, intellectual capacity, and information processing.

A second group of rating instruments was designed to measure the secondary symptoms that accompany organic brain disease such as depression, anxiety, paranoia, apathy, and withdrawal. Following is a brief description of the specific instruments included in each of the two categories.

Psychological and Psychophysical Performance Tests.—The *Wechsler Adult Intelligence Scale*[11] was utilized as a screening instrument and also as a means of evaluating treatment effects. The WAIS was administered prior to treatment and the Wechsler Bellevue Form II (WBII), which served as the equivalent form of the WAIS, was administered on the second day following treatment. The *Guild Memory Test*[11] is designed to be administered in conjunction with the WAIS or WBII. Each of five types of memory function measured by the Guild, ie, initial recall of meaningful verbal material, retention of meaningful verbal material, initial associative memory, retention of newly formed associations, and nonverbal memory, were examined for pre-post change.

In order to provide comparability with the original study by Jacobs et al and their ongoing research, the *Wechsler Memory Scale* (WMS)[13] and the *Bender-Gestalt Memory Phase*[14] were included in the test battery. In addition to computing the memory quotient, scores on each of the seven subscales of the WMS were computed as outcome measures reflecting different aspects of memory or cognitive function. The Bender-Gestalt was first administered in standard fashion, followed by administration of the memory phase. Both the standard administration and the memory phase were repeated utilizing Canter's Background Interference Procedure (BIP).[15] The BIP has been shown to increase the sensitivity of the Bender-Gestalt to defects in perceptual motor function associated with organic brain disorder.[15,16]

The four tests noted above were administered only twice, on the day prior to treatment and on the morning of the day following the final treatment session, as in the original Jacobs et al[1] design. In contrast, a repetitive test battery was administered on 11 separate occasions, ie, four times prior to treatment, on the 2nd and 14th days of treatment, one day after treatment, and at one, two, three, and eight weeks following treatment. The purpose of the four pretreatment testing sessions was to minimize the influence of practice effects and to familiarize subjects with the tests and thereby reduce any anxiety associated with test-taking. Also, multiple pretreatment assessments were thought to provide some control for the variability in test performance that has been reported to characterize elderly subjects.

The repetitive battery consisted of seven measures. *Finger-tapping speed* was determined by having subjects depress a key with the index finger as many times as possible in a 15-second interval. The task was intended to provide a basic measure of motor speed. The disparity between finger-tapping speed with the dominant and nondominant hand has been considered a crude index of organic impairment. Finger-tapping speed has also been used to assess mild to moderate organic pathology among geriatric patients,[17] and poor performance on this task has been associated with various circulatory disorders.[18] The *cross-out test* measures the speed with which a subject can find a well-known symbol embedded in a mass of material. The 150-second task is to cross out every digit in a row that is identical to the digit circled in that row.[19] The measure has a high loading on the cognitive factor identified by French et al[20] and others as perceptual speed. In the *hidden word test*, the task of the subject is to find as many four-letter words as possible embedded in 22 lines of continuous capital letters.[19] The measure loads very highly on the factor identified by French et al[20] as speed of closure. The *memory for faces test* has, as do the two previous measures, 20 alternate forms in the Moran and Mefferd series of repetitive psychometric measures.[21] The task involves two trials; in each the subject is exposed for 60 seconds to a composite stimulus panel of 16 facial photographs. Immediately after exposure the subject is presented a response panel composed of 32 photographs and asked to identify the 16 faces previously presented. The *first and last names test* is a measure of the factor identified by French et al[20] as associative memory. Subjects were given 120 seconds to inspect a list of ten paired first and last names. Each subject was then presented with a list of last names only and asked to provide the first name corresponding to each. Twenty alternate forms of the *digit span task* developed by Moran and Mefferd and colleagues[22] were employed. The task is a measure of the factor identified by French et al[20] as memory span. The *Spokes Test* is a modification of the Trail-Making Test of Reitan,[23] a standard neuropsychological measure of organic brain dysfunction.

In addition to the seven repetitive measures, the Friedhoff Task Behavior Scale[24] was completed by the examiner after each testing session.

Symptom Rating Scales.—The symptom rating scales were administered on the same days as the repetitive test battery. The *Nurse's Assessment of Global Symptomatology* is a 20-item behavioral assessment scale that is completed by a research nurse. The items called for global judgments of the subject's behavior on four-point scales. Item content was influenced by the findings of a number of investigators with behavior rating scales designed for use with geriatric patients.[25-29] The *Modified Inventory of Psychic and Somatic Complaints* (MIPSC) represents a modification of the Inventory of Psychic and Somatic Complaints utilized in the NIMH collaborative depression studies.[29] The key items comprising relevant factors from those studies were retained. Additional items were drawn from existing geriatric rating scales or were composed on the basis of symptomatological descriptions of senile deterioration provided in standard psychiatric references. The *Modified Patient Mood Scales* represents a modification of the Mood Scales from the NIMH collaborative depression studies.[28] Modification was accomplished as with the MIPSC. The *Symptom Checklist* was compiled with assistance from the Navy Experimental Diving Unit in Washington, DC. The investigators composed a list of physical symptoms to be systematically checked by a physician to monitor physiologic changes that might occur as a result of exposure to either normobaric or hyperbaric oxygen. This checklist was incorporated into several of the forms. *Global ratings of improvement* were made by study psychiatrists and nurses on nine-point scales from "very much improved" to "very much worse."

Statistical Analyses

For those measures that were administered only twice, ie, immediately prior to and immediately after treatment, treatment effects were evaluated by means of a one-way analysis of covariance. The covariates in these analyses were the pretreatment or initial scores. When a covariance F ratio revealed significant treatment effects, a Tukey (b) range test[30] was performed to see where the significant differences were among the four treatment groups. Unequal slope tests were also routinely performed both to assess homogeneity of regression and to determine if the treat-

Table 5.—Outcome of Subjects Started in Treatment

Outcome	Normobaric		Hyperbaric	
	Experimental	Control	Experimental	Control
Completed 15 days	21	21	20	20
Refused further treatment	4	1	1	0
Dropped for medical reasons	0	1	4*	1
Terminated because of deteriorating mental condition	0	0	2	1
Total	25	23	27	22

*Includes two subjects dropped because of elevated blood pressure, one because of ear problems, and one because of tissue swelling.

ments had differential effects as a function of initial level of psychopathology. The unequal slopes or pre-post regressions might indicate, for example, that hyperbaric oxygen was a good treatment for a mildly deteriorated patient but a poor treatment for a more severely deteriorated patient.

A more complex statistical approach was used for the psychological and symptom measures that were administered at frequent intervals throughout the study. A mixed-model repeated measurement design adapted from Winer[11] provided an overall test of treatment effects, with ratings for the various time periods averaged over time. This model also provided a separate test of differential treatment effects over time. For example, a significant treatment by time interaction might indicate that hyperbaric oxygen was especially beneficial early in treatment whereas normobaric oxygen showed its major effects later in treatment.

RESULTS

Terminations From Treatment

Table 5 indicates that once subjects got through the acclimation phase they were likely to remain in the study and complete 15 days of treatment. Although we had been led to expect some physical difficulties such as the "bends" with the hyperbaric group, whose subjects breathed a nitrogen-oxygen mixture, these fears did not materialize. Four subjects terminated treatment for medical reasons in the hyperbaric oxygen group—two because of elevated blood pressure, one because of an ear problem, and one because of tissue swelling.

Examination of the Symptom Checklist also disclosed surprisingly few treatment emergent or treatment-related symptoms. Four of the hyperbaric oxygen subjects who remained in the study complained of some hearing difficulty early in treatment, but more serious problems such as pulmonary and circulatory disturbances occurred rarely and with equal frequency among the normobaric and the hyperbaric subjects.

Results After Two Weeks of Treatment

There were eight significant treatment differences among the four groups after two weeks of treatment (Table 6). Eight significant findings of a total of 101 tests is hardly impressive and could be due to chance alone. The final adjusted means noted in Table 6 are derived from ratings scored in a direction consonant with the variable descriptions in this table. Hence, the values listed for "correct recall of faces" are the number of correct recalls. Similarly, for the variable "shows annoyance" the values listed are the amount of annoyance displayed by the subjects and rated on four-point scales from "not at all" to "extremely." On the basis of ratings by the test examiners and study nurses, there was some suggestion that after two weeks of treatment, the normobaric air subjects were more hostile and asocial than other subjects in the study. We are not sure how to interpret this finding except to note that there was resentment among some of the normobaric subjects about their not being assigned to hyperbaric treatment, which was the preferred treatment for most subjects when they applied for entrance into the study.

There were also only three significant unequal slopes tests, and these were on quite dissimilar variables. Plots of the pre-post regressions for the four treatment groups on these variables did not show any evidence of differential treatment effects as a function of initial level of psychopathology or cognitive impairment.

A special point was made of analyzing group differences immediately after treatment to provide a direct replication of the initial Jacobs et al[4] study. It is readily apparent the results of the present study did not replicate those of Jacobs et al. To emphasize this point, the Figure compares the mean pretreatment and posttreatment scores on the Wechsler Memory Quotient of hyperbaric experimental and control subjects in our study with those in the Jacobs et al study. The Figure shows that our results failed to replicate the improvement in memory quotient scores that Jacobs and co-workers noted for their hyperbaric oxygen subjects.

Differences Averaged Over Time

In these analyses, the individual ratings for each subject at each time period were summed and an average score was derived. Ratings made at day 5 of the seven-day pretreatment or acclimation phase served as the covariates in these analyses. Group differences on these average scores were then tested for statistical significance. This is an especially discriminating approach for identifying small but consistent differences among the groups that accrue over time. The results in Table 7 indicate that there was a consistent trend for subjects undergoing hyperbaric treatment to rate themselves as feeling less anxious, less depressed, and less fatigued than their normobaric counterparts. A more detailed examination of these ratings at each time period including day 5 of the acclimation phase disclosed that these differences first became apparent during the acclimation phase, before treatment had begun, and not only persisted but became more pronounced as treatment progressed, extending up to and including the final evaluations made eight weeks after treatment was terminated. We can only speculate that there must have been some sort of halo effect associated with the hyperbaric treatment that led these subjects to expect positive results from this treatment, and that this expectation was more persistent than the usual two- or three-week placebo response. It will be recalled that normobaric treatment was administered in a hospital room whereas considerably more mystique surrounded hyperbaric treatment, which was given in a large, steel compression chamber with air locks on the doors and that inwardly resembles a spaceship or submarine.

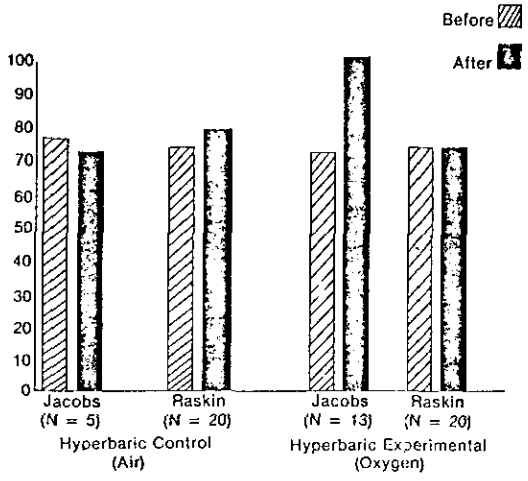
Differential Effects Over Time

The repeated measurement model also provided a test of differential treatment effects at various time periods in

Table 6.—Significant Group Differences on Behavioral and Symptom Measures After Two Weeks of Treatment

Variable	Rater	Final Adjusted Mean: Normobaric O_2 (1)	Normobaric Air (2)	Hyperbaric O_2 (3)	Hyperbaric Air (4)	F	Difference
Psychometric performance							
Correct recall of faces	Examiner	5.91	4.02	3.93	3.29	4.29*	1-2,3,4‡
Finger tapping, nondominant hand	Examiner	59.73	55.89	49.21	52.20	2.99†	1-4,3
Behavioral ratings							
Attention to task	Examiner	2.87	2.43	2.89	2.60	5.64*	3,1-4,2
Shows cooperation	Examiner	2.81	2.46	2.74	2.78	3.43†	1,4,3-2
Shows annoyance	Examiner	1.25	1.43	1.00	1.12	2.91†	2-4,3
Participates in social activities	Nurse	1.55	1.31	1.92	1.60	2.94†	3-2
Expressed concern with *health*	*Nurse*	1.55	1.13	1.17	1.46	3.03†	1,4-2,3
Self-ratings							
Carefree	Subject	1.98	1.64	2.07	1.69	4.74*	3,1-4,2

*Significant at .01 level (two-tailed).
†Significant at .05 level (two-tailed).
‡Indicates that normobaric oxygen subjects had significantly higher recall of faces scores than subjects in the other three groups.



Comparison of mean memory quotient scores for experimental and control subjects before and after hyperbaric treatment in studies by Jacobs et al[5] and Raskin et al (current).

the study. There were 11 significant treatment by period interactions. However, when these were plotted to discern trends over time, it became apparent that although there was considerable variability in the behavior of our subjects, this variability did not show a consistent pattern across variables and was probably not related to treatment effects per se.

COMMENT

Simply put, the results of this study failed to sustain the view that oxygen treatment, under either hyperbaric or normobaric conditions, has beneficial effects on cognitive impairment in the elderly. Further, a number of criticisms made of prior studies that failed to replicate Jacobs and associates' initial observation do not seem to apply to the present study. The Goldfarb et al[3] and, to a lesser extent, the Thompson et al[4] studies have been criticized for including a significant number of severely deteriorated subjects in whom one would not expect to see much improvement, even with a relatively potent treatment. However, the subjects in the present study were all ambulatory and living in the community. Further, on the basis of their Wechsler Memory Quotient scores (Table 2), they were comparable to the subjects in the Jacobs et al[5] study and clearly less deteriorated than the subjects in the Goldfarb et al[3] study.

The possiblity of differential treatment effects as a function of initial severity of illness was also put to a direct test in both the present study and in the study by Thompson and associates.[4] In neither study was there evidence that less severely ill subjects will show a better response to hyperbaric oxygen treatment than those more severely ill.

The study by Goldfarb et al[3] has also been criticized because many of the subjects were Jewish and some became agitated at entering the hyperbaric chamber, which they likened to the gas chambers in Nazi Germany. In our study there appeared to be quite an opposite reaction, with evidence of a halo effect occurring among subjects who received hyperbaric oxygen. It will be recalled that both the hyperbaric oxygen and the hyperbaric air, or control, subjects reported feeling less anxious and depressed than subjects who were assigned to the two normobaric groups. Hence, to the extent one might expect results on the evaluation instruments to be influenced by the subjects' expectations and other psychological factors, the results should favor the hyperbaric subjects in our study.

The argument has also been made that hyperbaric oxygen treatment is especially beneficial for a subgroup of organically impaired subjects, namely those with cerebrovascular disease or cardiopulmonary insufficiency in which oxygen delivery to the brain is impaired. This is consistent with the view of Jacobs et al[5] that the beneficial effects of hyperbaric oxygen treatment are due to the existence in some individuals of fairly extensive numbers of cortical cells that were marginally hypoxic, ie, "they may be

Table 7.—Significant Group Differences When Behavioral and Symptom Measures Are Averaged Over Course of Study

Variable	Rater	Final Adjusted Mean: Normobaric O_2 (1)	Normobaric Air (2)	Hyperbaric O_2 (3)	Hyperbaric Air (4)	F	Difference
Behavioral ratings							
Attention to task	Examiner	2.80	2.57	2.80	2.54	3.39*	1,3-2,4‡
Expressed concern with health	Nurse	1.54	1.20	1.21	1.44	3.85*	1-3,2
Difficulty making decisions	Nurse	3.62	4.05	4.37	4.19	3.84*	3,4-1
Self-ratings							
Anxiety	Subject	1.65	1.65	1.39	1.36	4.77†	2,1-4,3
Depression	Subject	1.55	1.68	1.35	1.36	7.12†	2,1-4,3
Fatigue	Subject	1.70	1.68	1.31	1.36	8.68†	1,2-4,3
Carefree	Subject	1.88	1.71	1.99	1.76	3.49*	3-4,2
Friendliness	Subject	2.47	2.23	2.56	2.46	4.35†	3,1,4-2

*Significant at .05 level (two-tailed).
†Significant at .01 level (two-tailed).
‡Indicates that both the normobaric oxygen and the hyperbaric oxygen subjects showed greater attention to task than the two control groups.

receiving enough oxygen to remain anatomically alive, but not enough to function effectively." Thompson et al[5] divided their subjects into two groups, those with cerebrovascular disease and those with cortical atrophy. Assignment to these categories was made on the basis of a medical history, a neurological examination, and, in ten cases, the results of pneumoencephalography. These authors failed to find a differential effect of hyperbaric oxygen favoring their subjects with cerebrovascular disease. However, they also noted that their cerebrovascular subjects had stabilized or chronic neurologic deficits and the ischemic damage in these subjects was probably irreversible. Thompson and colleagues, therefore, left the door open to the possibility of beneficial effects of repeated exposure to hyperbaric oxygen in subjects with acute cerebral ischemia.

In the present study, efforts were also made to isolate subgroups of subjects who might be expected to show an especially good response to oxygen treatment. First, our sample was divided into those deemed to have cerebrovascular disease (N = 40) and those deemed not to have cerebrovascular disease (N = 42). These assignments were made jointly by a study psychiatrist and neurologist on the basis of a medical history and a neurological examination. Information from these sources was recorded on a special form listing the major signs or symptoms that have been associated in the past with evidence of cerebrovascular disease, eg, history of stroke and hypertension. A checklist was also provided to note other signs of vascular disease, such as a thickening or twisting of specified peripheral arteries, eg, carotids, brachial, and radial. On the basis of this admittedly crude attempt at differentiating subjects, we also failed to find evidence of especially beneficial effects of oxygen treatment for those subjects judged to have cerebrovascular disease. It may be well to point out that at the time this study was undertaken some of the newer nonintrusive diagnostic tools for differentiating and assessing cerebral pathology, such as computerized axial tomography and the xenon inhalation technique for the measurement of cerebral blood flow, were in limited supply and not generally available.

The CO_2 loading test[11,12] was also used as a means of examining differential treatment effects. This test consists of exposing subjects for five minutes to a 5% CO_2 and 95% O_2 mixture and then dividing them into two groups, those who did significantly better (N = 46) and those who failed to improve or did worse (N = 36) on a series of psychological tests following exposure to CO_2, which is a powerful vasodilator. The measures utilized for this purpose were derived from the seven repetitive psychological and psychomotor tests. Again, contrary to expectations, the CO_2 responders did not show an especially good response to oxygen treatment under either normobaric or hyperbaric conditions. In fairness, however, to the rationale Jacobs et al[5] have provided for hyperbaric oxygen treatment, we are also not certain our cerebrovascular subjects could legitimately be classified as suffering from acute cerebral ischemia. Seventy-eight percent of our subjects were reported by their families to have experienced significant memory loss at least one year prior to their admission to the study. Consequently, we have not ruled out the possibility that the advent of new and more sophisticated techniques for identifying early signs of cerebral ischemia may make it possible to identify individuals who would benefit from repeated exposure to oxygen treatment.

A report by Salzman and Shader[13] of a differential response to diazepam among elderly male and female subjects prompted an examination of sex differences in our study. For this purpose, we focused on the psychological and psychomotor test variables administered prior to and immediately following treatment. Again, the results were disappointing, with only one significant treatment by sex interaction of 32 tests. Female normobaric control subjects performed significantly better than their male counterparts on the digit span subtest of the WAIS.

We also identified a small group of hyperbaric oxygen patients (N = 4) and an equally small group of normobaric oxygen patients (N = 3) who showed a ten-point or more improvement on the Wechsler Memory Scale after 15 days of treatment. These patients were compared with each other and with the hyperbaric and normobaric oxygen patients who failed to show this amount of WMS improvement on background variables, such as age and sex, and on

Table 8.—Results of Visual Acuity Tests Prior to Treatment and After 15 Days of Treatment*

	Normobaric		Hyperbaric	
	O_2	Air	O_2	Air
Improved	6	7	7	4
No change	5	8	5	4
Worsened	10	6	8	12

*$\chi^2 = 4.811$, $df = 6$; not significant.

20 medical history and neurological examination variables. Included in this latter category were a history of hypertension, head trauma, and cardiovascular dysfunction. On the basis of both visual inspection and statistical analyses of these data, we were unable to identify any meaningful traits that distinguished either the pooled sample of normobaric and hyperbaric oxygen responders or the smaller sample of hyperbaric oxygen responders.

As a final aside, there was one report of improved visual acuity in a few elderly subjects following hyperbaric oxygen treatment.[4] The beneficial effect of hyperbaric oxygen was presumed to be due to improved retinal blood flow. Lacking more sophisticated equipment, we used a Snellen eye chart to test visual acuity in our subjects immediately prior to and immediately following treatment. As noted in Table 8, there was no evidence of improved visual acuity in our experimental subjects following 15 days of exposure to oxygen under normobaric and hyperbaric conditions.

Although this study does have some limitations, particularly in regard to the differentiation of subjects with cerebrovascular disease from those with cortical atrophy, the results are nevertheless convincing in highlighting the limitations of hyperbaric and normobaric oxygen as treatments for cognitive deficits in the elderly. Subjects who entered this study had well-documented evidence of memory problems but were still sufficiently intact to reside in the community and to respond meaningfully to an intelligence test and to other psychological and psychometric tests. On the basis of the findings of Jacobs et al[1] and others,[2-6] one would have expected many of these patients to show a favorable response to hyperbaric oxygen treatment. The study findings clearly indicate that this was not the case.

This investigation was supported in part by grant MH 24337 from the National Institute of Mental Health.

Hyperbaric treatment was administered under the direction of Theobald Reich, MD, at the Institute of Rehabilitation Medicine (IRM), New York University School of Medicine. Pulmonary function tests were conducted at IRM by Albert Haas, MD, Chief of Pulmonary Medicine. The technical staff responsible for operation of the hyperbaric chamber was supervised by Charles H. Reustle and included Howard L. Carswell and Ralph E. Garcia. Nurses who accompanied patients during hyperbaric exposure were Betty Hunnum, Ronnie DeCarlos, and Michelle Aaronson. Assistance in conducting psychological testing and behavioral ratings was provided by Cathy Clark, Judy Moshinski, and Hyacinth Thompson of the Neuropsychopharmacology Research Unit, New York University Medical Center.

The statistical analyses were performed at the Computer Systems Branch of the National Institute of Mental Health, and at the George Washington University Biometric Laboratory, which was supported in part by grant MH 22019 from the National Institute of Mental Health.

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The Measurement of Oxygen Tension in Healing Tissue

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Abstract

Observations have been made of the oxygen micro-climate during connective tissue regeneration in rabbit ear chambers. A modification of standard ear chambers is described which enables non-destructive measurements with oxygen micro electrodes to be made on the tissue. Wound 'dead space' had a very low oxygen tension (less than 3 mm Hg). Macrophages were the only cells which appeared to tolerate such low tension. Actively dividing fibroblasts were confined to regions where the tension was more than 15 mm Hg. Collagen formation appeared especially at tensions between 15 to 30 mm Hg.

Oxygen breathing increased the intercapillary oxygen gradient especially in the zones of active cell division.

Changes in the microcirculation produced very marked alteration of the oxygen climate in the tissue.

Introduction

It has been known for some years that lowering the oxygen tension in respired air may adversely affect wound healing in human and animal subjects [UTKINA, 1964]. Conversely exposure to high ambient oxygen concentrations may accelerate healing and increase the strength of scar tissue formation [BECKHAM and HITCHCOCK, 1965; LUNGREN and SANDBERG, 1965]. Bone formation and repair has also been shown to be affected by oxygen concentration. COULSON, FERGUSON and DIEHL [1966] demonstrated that exposure to hyperbaric oxygen accelerated the healing of bone fractures and CATER, EZRA and SILVER [1969] found that the oxygen tension in the vicinity of growing bone autografts was lower than that in the surrounding soft tissue. More fundamental studies on the effect of oxygen tension on fibroblast division and collagen synthesis have been carried out by a number of workers who have demonstrated that collagen synthesis is

initiated in high density stationary cultures of fibroblasts in suspension, [MAXWELL and GLINOS, 1966; GLINOS, 1967] where oxygen concentration was found to be very low [GLINOS, VAIL and BARTOS, 1968]. Studies on the oxygen environment in healing tissues by means of chronically implanted oxygen electrodes have been made by HUNT [1964], GOLDSTICK and HUNT [1966], HUNT, GOLDSTICK, ZEDERFELDT and CONOLLY [1967] and HUNT, ZEDERFELDT and DUNPHY [1968] and these have shown that average conditions during wound repair may be by no means optimal for fibroblast division and collagen formation. In view of the steep gradients between the oxygen tension in a capillary and that obtaining in the tissue a few microns away in tissues with a high oxygen uptake, it seems likely that much of the volume of a traumatised region may be existing in conditions which are far from conducive to healing. The experiments which form the basis of the present paper were carried out in order to study the oxygen micro-climate in various parts of a tissue defect during natural repair and it is proposed at a later stage to attempt to correlate this micro-climate with a detailed study of the microcirculation.

In order to study tissue repair under direct vision and in a relatively controlled situation observations were made during vascularisation of a rabbit ear chamber. The original studies were carried out with a modified Sandison-Clark chamber [see SILVER, EZRA and CATER, 1969] and later studies were continued with a chamber modified from the design described by SUMNER WOOD [1966] which enabled measurements to be made without disruption of the tissues.

Methods

Animals

Adult half-lop eared rabbits weighing from 2.5 to 4 kg were used for implantation of transparent methacrylate (Perspex, I.C.I. and Kleer-Tuf, Goodyear Corp.) ear chambers. This breed is derived originally from crossing full-lop eared rabbits with Belgian hares. The ears are pendulous and measure from 20 to 25 cm in length and 10 to 15 cm in width at the widest part.

Operation

The animals were anaesthetised either with Pentobarbitone sodium 20 mg/kg i.v. or with Fentanyl citrate (0.155 mg/kg) and Fluanisone (5 mg/kg) (Hypnorm, Crookes Laboratories Ltd., Basingstoke, England) given intramuscularly. This latter drug produces insensitivity to pain and deep tranquillisation. The rabbit shows sluggish righting reflexes although it

will usually lie passively in any position in which it is placed. Although respiration is depressed the danger of respiratory arrest which so commonly occurs in the rabbit under Pentobarbitone rarely occurs with Hypnorm.

The ear chambers were inserted into the ears with full aseptic precautions by the methods already described by SANDISON [1928], CLARK and CLARK [1942] and SUMNER WOOD [1966]. Great care was taken to ensure that minimal trauma was inflicted on the cartilage of the ear in order to avoid subsequent necrosis.

Ear Chambers

1. Modified Sandison-Clark chamber. This chamber was adapted in the manner described by SILVER *et al.* [1969] so that a number of areas of tissue within the chamber were accessible to investigation by means of electrodes. These latter could be fitted into a special socket that was periodically attached to the chamber. The method proved to be useful only for siting experiments and was abandoned in favour of a modification of the Wood chamber when more detailed studies were undertaken.

2. Modified Wood chamber. The basic design of this chamber was retained [see WOOD, 1966] but the plug was tapered to allow for easier insertion through the ear and the glass cover slip was replaced by two 300 gauge (75 μ) polyester sheets (Melinex, I.C.I.) each of which contained an excentrically placed hole. A disc of Teflon film approximately 3 microns thick was located between the cover slip and the chamber cavity (fig. 1).

After implantation the ear chambers were examined daily with a low power binocular microscope and were not disturbed until a zone of advancing vascularisation was observed at the edges of the chamber. As soon as this growth was established and was shown to be free of infection, measurements of oxygen tension were started.

Electrodes

Three types of electrodes were used in conjunction with the chambers:

1. A macro, Clark-type electrode [CLARK, 1956] with a 1 to 5 μ cathode as described by SILVER *et al.* [1969] which fitted into a special well that could be attached to a modified Sandison-Clark ear chamber. This electrode could be manoeuvred by rotating it in its housing so that it was aligned with holes in the cover slip, into which the cathode surface projected. The chief limitation of the system was that the resolution of the electrode was relatively poor and the electrode itself could not be made to approach nearer than about 25 μ to the tissue whose oxygen climate was being investigated. Thus the electrode measured a pooled oxygen tension and was useful only for identifying relatively large differences in regional oxygen tension.

2. Membrane-covered micro-electrodes. Preliminary investigations within the growing edge of tissues in ear chambers were undertaken with a membrane-covered 'micro-Clark electrode' of the type described by SILVER [1965]. These electrodes were employed by inserting them into the ear chamber after the cover slip had been carefully removed under a layer of liquid paraffin (heavy mineral oil). Although measurements of tissue PO_2 could be made with this procedure it was rarely possible to replace the cover slip on the chamber without damaging the very fragile precapillaries in the edge of the advancing tissue.

3. A non-destructive system was devised in which the depth of the chamber was reduced from 25 μ to 12 μ and the cover slip was separated from the tissue by a very thin layer of

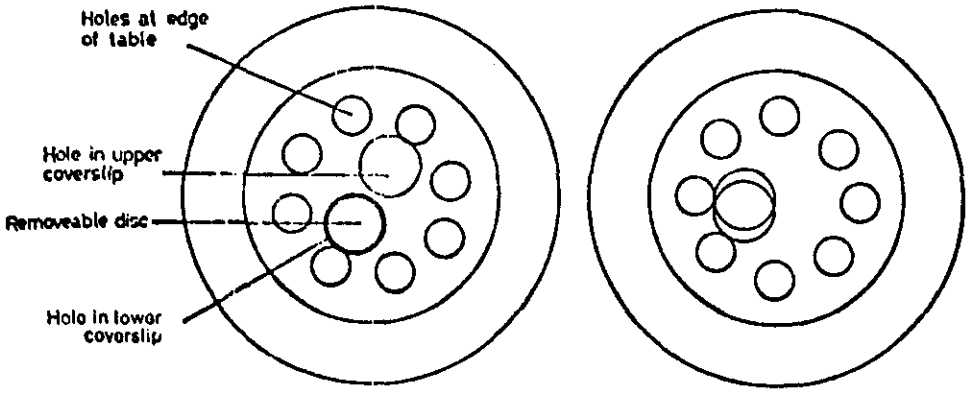

Fig. 1a *Fig. 1b*

Fig. 1a. Plan of ear chamber seen from above with the cover slips in the normal position. *Fig. 1b.* Chamber plan as in (a) but with cover slips rotated and disc removed to allow for measurement of PO_2.

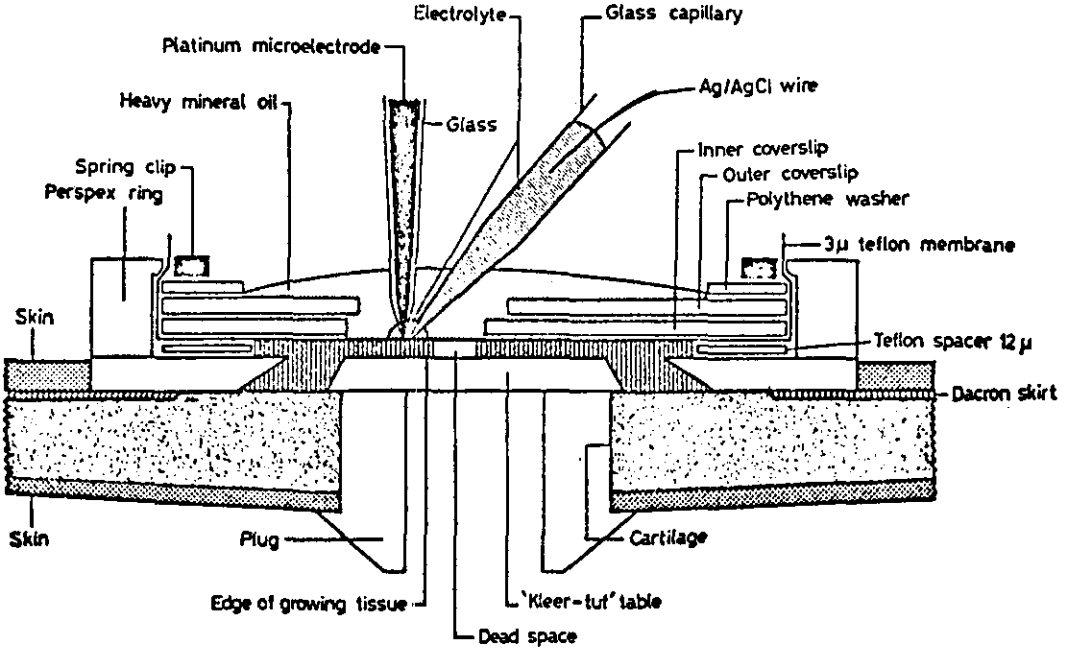

Fig. 1c. Schematic cross-section of ear chamber to show the arrangement of external electrodes during a measurement of local PO_2. The drawing is not to scale and the ear chamber components have been slightly separated for clarity.

Teflon which was approximately 3 μ thick. In order to make measurements the cover slips were rotated under mineral oil until the two holes coincided but the Teflon remained in place. An open-tipped platinum-in-glass micro-electrode with a 1 μ point was lowered through the oil until it touched the surface of the membrane. This electrode was accompanied by a micro pipette which carried electrolyte and served as a salt bridge to an indifferent silver/silver chloride electrode. A very small drop of electrolyte was suspended between the electrode and the pipette and adhered tightly to them (fig. 1c). When the electrode was moved across the membrane the electrolyte moved with it. This system was polarised either with a constant DC voltage or with short pulses of the order of 1.5 m sec. When it was necessary to make observations in regions containing what appeared to be especially steep oxygen gradients the electrode was allowed to penetrate the membrane and to enter the tissue directly. This procedure appeared to disturb the chamber contents less than removal of the cover slip and insertion of the electrode as described in (2) above.

Positioning of electrodes in relation to blood vessels and other structures within the ear chamber was carried out under direct vision using a stereobinocular microscope with a long working distance. The lighting source was carefully screened with heat absorbing filters so that radiation from the lights would not produce changes in the capillary bed, or beating and changes in metabolic rate of the tissue within the chamber.

Results

The first signs of new tissue growing onto the table of the chamber from the hole in the ear appeared 5–10 days after implantation. The arrangement of the cellular elements, as determined from low power electron micrographs of perfusion fixed materials, was as follows:

a) both surfaces of the chamber were lined with histiocytes which also formed the extreme edge of the growing tissue.

b) rounded cells which could be identified as fibroblasts were situated between the histiocytes and the first capillary arcades.

c) blind ended capillary buds were distributed among the fibroblasts.

d) behind the capillary arcades the fibroblasts were elongated and associated with clearly identifiable collagen fibres.

Major Regional Differences in PO_2 Observed with the First Electrode System

After insertion of an ear chamber the oxygen tension in the fluid within the chamber, which may be considered equivalent to the 'dead space' of a wound, fell to very low levels and persistently showed tensions between zero and 2 mm/Hg. When a micro-circulation was firmly established at the edge of the chamber the PO_2 of fluid over this region rose to an average of 30–40 mm/Hg. This value was slightly below the general oxygen tension reading

which was obtained over a fully established ear chamber, where the tension was of the order of about 45–50 mm. Another, and very obvious difference between the growing chamber and the fully established tissue was the response to oxygen breathing. In a growing chamber the change in oxygen tension when 100% oxygen was breathed was relatively slight and took as many as 45 or more minutes to reach a new steady level. In an established chamber the rise of tension was much greater and a new steady state was reached relatively rapidly. Similar differences in response have been found by HUNT *et al.* [1968] in gross surgical wounds at different stages in the healing process.

Implantation of bone into a chamber caused a marked reorganisation of the micro-circulation and also changed the oxygen tension in the vicinity of the graft. This change occurred only if the graft was viable and consisted of a fall in oxygen tension over the bone and along its growing edges together with a reduced increase in oxygen tension following oxygen breathing.

Tissue Oxygen Gradients Observed with Micro Electrodes

Micro electrodes were inserted into chambers only when invasion of the chamber from the periphery was well established. Nevertheless the oxygen tensions found in the chamber dead space at distances of more than 120–140 μ beyond the nearest capillary arcade were always less than 3 mm/Hg.

Tissue Structure and PO_2 at the Growing Edge

The first cells that could be identified in electron micrographs in the van of the advancing tissue were histiocytes and these appeared to be able to grow into regions where the oxygen tension approximated to zero. The first fibroblasts were seen nearer the capillary arcades at a distance of some 70–80 μ from the nearest circulating blood. In this region the PO_2 was slightly higher and was usually found to be about 5 mm/Hg. No divisions were observed in fibroblasts in this zone. Nearer the capillary loops the oxygen tension rose until in the position where it reached 25–30 mm/Hg large numbers of dividing fibroblasts could be found. There was very little evidence of fibre formation in this zone although minute strands of collagen could be identified under polarised light in association with the walls of capillary buds. The gradient of oxygen tension from the capillary to the growing edge of the tissue was rather steep and showed a particularly rapid fall in the

dividing fibroblast zone in front of the capillary. This gradient was usually from 80–90 mm/Hg PO_2 directly over the capillary wall to around 20 mm/Hg at a distance of about 50 μ from the vessel. Beyond this point the gradient became less steep in most situations but in others it continued outwards with the same slope down to a value of about 8–10 mm/Hg. No clear reason for this difference has yet been observed.

Behind the advancing capillary loops the zone of dividing fibroblasts was continued for a short distance and then gave way to a region where obvious collagen formation and elongation of the cells became apparent. In this zone the PO_2 was lower than immediately adjacent to the capillaries but the gradient of PO_2 between the capillaries was less steep. In the region where large fibres were forming the PO_2 appeared to be between 15 and 30 mm/Hg. Towards the periphery of the chamber where there was a well established collagen stroma the intercapillary distances were greater than near the growing edge and the oxygen gradients were comparatively flat. This flattening of the gradients corresponded with the zone observed with the large electrode system in which there was a relatively high 'average' PO_2.

Response to Oxygen Breathing

In the central 'dead space' zone there was little or no change in oxygen tension when the rabbits breathed oxygen even for long periods (up to 45 min). Similar lack of response to oxygen breathing was observed in the outermost region of living cells 120 μ from the nearest advancing capillaries.

Electrodes in contact with capillaries in which there was circulating blood always showed an increase in oxygen tension when the animals breathed pure oxygen but the diameter of the capillaries underwent a reduction when the PO_2 rose above 140 mm/Hg and this constriction was maximal at tensions around 300 mm/Hg. From a limited number of measurements it appeared that the reduction in diameter was of the order of 30%. The large increase in arterial capillary PO_2 which accompanied oxygen breathing was not reflected in the PO_2 of the tissue at the growing edge. The main effect of increasing arterial PO_2 was to increase the steepness of the PO_2 gradient within the tissue so that whereas under air breathing conditions the gradient ran from about 90 mm/Hg to zero in 150 μ, after 5 min of oxygen breathing the gradient ran from 450 mm/Hg or more to zero in approximately the same distance. The major fall in PO_2 occurred between the capillary and the outer edge of the dividing fibroblast layer at a distance of approximately

70 μ from the capillary. Prolonged exposure to oxygen of the order of 45 min resulted in a small increase in the oxygen tension at a distance of 150 μ from the capillary.

Measurements of oxygen tension under similar conditions in regions of the ear chamber where repair was complete and extensive fibrosis had occurred revealed a very different pattern of oxygen gradient. Under quiet conditions the intercapillary distances were large and might be as much as 200 microns but during reactive hyperemia many more capillaries appeared which later closed down again. The average PO_2 gradients when the animals were breathing oxygen were relatively shallow and when oxygen was breathed the tissue PO_2 rose rapidly in spite of constriction of the capillaries similar to that seen at the growing edges. Nevertheless the increase in tissue PO_2 was not by any means equivalent to the increase in blood PO_2 so that some change in the intercapillary PO_2 gradient did occur. It was clear however that the demand for oxygen in the fibrosed tissue was very much less than that in the zones of active cellular proliferation.

Similar measurements made in the intervening zone between the growing edge and the fully established parts of the chambers showed that oxygen uptake during fibre formation, although less than that during cell proliferation, was clearly more than that in the older tissue.

Oxygen tension gradients remained stable only if the animal was undisturbed. Sudden loud noises caused rapid blanching of the capillary bed and drastic falls in oxygen tension followed immediately. The falls were particularly rapid in the region of the advancing edge of the tissue. Similar effects were produced by injections of adrenaline i.v. (1 μg/kg). If a chamber became infected the capillaries dilated and the blood flow slowed in the normal inflammatory response. A few observations under these conditions indicated that the oxygen tension fell to very low levels quite close to the capillaries. Lowering of blood pressure by the inhalation of amyl nitrite caused rapid falls in PO_2 of healing tissue even though the arterial PO_2 did not change. This indicated the very close link between capillary perfusion rates and the tissue PO_2 which was particularly clear in regions of high oxygen uptake.

Discussion

The conditions obtaining in healing tissues are of interest both fundamentally and in clinical medicine. While it has been realised for some time that oxygen is essential for satisfactory wound healing and that patients

with vascular disease or impaired pulmonary function heal slowly, no explanation has been available until very recently in terms of cellular behaviour, to account for these observations. The major impetus in the search for factors which affect tissue regeneration has come from surgeons on the one hand and workers with tissue or cell cultures on the other. The observations reported in this paper are complementary to these two fields of interest in that they are made almost at the cellular level but the cells are part of organised, naturally regenerating tissue. It may be argued that the repair processes within a rabbit ear chamber are not necessarily the same as those occurring in a wound, if only because no epidermis is involved. While this may be true of the organisation of granulation tissue immediately underlying proliferating epidermis it is reasonable to suppose that fibroblast growth in a chamber will proceed in a manner similar to that which occurs in the depth of wounds.

The methods used here are also complementary to those which have been used in other types of investigation. HUNT [1964], HUNT *et al.* [1967] and HUNT, TWOMEY, ZEDERFELDT and DUNPHY [1967] have developed an ingenious system for measuring the PO_2 and other factors in healing wound on a relatively gross scale, and have studied the long-term changes which occur during repair processes. Their measurements have been made on 'wound fluid' and therefore represent an average of PO_2 in the dead space of the wound. While this information is of considerable value it obviously conceals a great deal of useful data which is probably relevant to the behaviour of cells in the wound. At the other end of the scale GLINOS *et al.* [1968] and UDENFRIEND [1966] have studied the conditions in tissue culture which promote or discourage the division of fibroblasts and their ability to form fibres. CHANCE in a series of very elegant experiments has studied the oxygen concentrations which are necessary for normal cellular respiration and has predicted the oxygen tension gradients that might be expected in some tissues [see CHANCE, SCHOENER and SCHINDLER, 1964]. The measurements made with micro electrodes in rabbit ear chambers fill the gap between the observations on gross wound healing and those on tissue cultures. It appears so far that most of the observations of the different groups of workers are consistent with each other although there may be some difficulty in interpreting the conditions under which collagen formation takes place naturally. It has been shown by UDENFRIEND [1966] that oxygen is necessary for the formation of collagen yet GLINOS *et al.* [1968] have results which suggest that the production of collagen may be a maturation phenomenon in response to conditions which are unfavourable to cell division.

The accuracy of the observations which are reported is clearly limited by the efficiency of the method of measurement. There appears to be some discrepancy between theoretical predictions of the volume of fluid from which an electrode draws its oxygen and experimental findings. On the basis of classical diffusion theory it is expected that 97% of the oxygen used by an electrode would diffuse from a sphere of a radius of approximately 150 times the radius of the electrode under steady state conditions [CATER and SILVER, 1961]. FATT [1964] has shown that for small electrodes of the order of 1 micron the actual distance from which 97% of the oxygen is drawn under experimental conditions is about 6 times the diameter of the electrode and this has been confirmed by other workers [see SILVER 1965, 1966; KUNZE, 1967, 1968]. An explanation for this may be that the electrical polyl-layers which are formed at the surface of the cathode during polarisation may constitute a very effective diffusion barrier which thus greatly improves the resolution of the electrode. The resolution becomes still better if voltage pulses are applied to the electrode and the current reading is made soon after the pulse is applied. If the pulse is of short duration the diffusion field reaching out from the electrode surface is very largely confined to the region of the polylayer and is therefore undisturbed by the influence of stirring artefacts. A disadvantage of the pulsed system is that high currents are obtained in oxygen-free situations, but the relative immunity of electrodes used in this way to electrophoretic deposition of protein makes the system valuable for use in conjunction with micro electrodes that are in contact with a tissue that is not electrically excitable [DAVIES and BRINK, 1942; WHALEN, 1969].

The presence of an electrode within the tissues will inevitably alter to some extent the conditions near its tip. It is one of the advantages of the ear chamber technique that the tissue is almost two-dimensional and that the position of the electrode vis-a-vis the capillary bed can be observed at all times under direct vision without actually penetrating or disturbing the tissue. Nevertheless the readings that were obtained when micro electrodes were embedded in the tissue were almost identical with those from micro electrodes lying against a Teflon film which formed the boundary of the tissue. This indicated (a) that very small electrodes in tissue cause minimal disturbance to oxygen diffusion and (b) that measurements with micro electrodes on the surface of very thin layers of tissue can give useful information.

Capillary blood flow is highly labile and is rapidly affected by a large number of factors including oxygen tension. It may be that the increased

slope of tissue PO_2 gradients which is seen after the raising of blood PO_2 results from reduced blood flow and a minimal increase in the amount of oxygen being transported to the tissues, even though it is at a higher tension. It is not therefore possible to make a general statement about the oxygen tension at a particular point in healing tissue except on a very short term basis. Newly formed blood vessels are extremely sensitive to circulating agents such as 5-hydroxy tryptamine and bradykinin, while hypovolaemia, lowering of blood pressure, changes in sympathetic tone, or infection can all drastically change the pattern of oxygen tension in healing tissue and it should be emphasised that the findings reported here are of a very preliminary nature.

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INERT GAS NARCOSIS

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INERT GAS NARCOSIS

ALBERT R. BEHNKE, JR.

The narcotic effect of nitrogen during the course of exposure in high pressure air atmospheres has remained obscure for more than a century. In the older literature dealing with caisson operations, the usual mood of workmen in a compressed-air atmosphere was euphoria. In scuba diving the expansive feeling at pressure depths is euphemistically referred to as "rapture of the depths."

Damant (1930) and Hill (1932) observed that deep-sea divers at depths of 270 to 300 ft (9 to 10 ATA) had difficulty in assimilating instructions and making decisions. Severe emotional disturbances, as well as loss of consciousness, were reported. In the 1932–1935 experiments conducted in the Harvard pressure chamber at 4 ATA, it was apparent that even at this relatively low pressure, individuals experienced varying degrees of euphoria with tendency to fixation of ideas accompanied by some impairment of fine manipulative procedures. Behnke et al. (1935), in reporting untoward reactions under seemingly favorable environmental conditions, attributed them to the narcotic effect of nitrogen in accord with the Meyer-Overton hypothesis that substances, generally with high lipid-to-water solubility ratios, were narcotic in varying degree.

Initial tests by Shilling and Willgrube (1937) conducted at air pressures of 4 to 10 ATA served to quantify the degree of impairment relative to gradations of pressure. Subsequently, tests by many others have provided systematic and comprehensive characterization of the narcotic action of nitrogen:

Edgar End (1938)—mental changes—difficult to exercise the quick decisions necessary for successful diving.
Kiessling and Maag (1960)—reaction time, motor coordination, and reasoning.
Adolfson and Maren (1965)—Mental and psychomotor performance.
Bennett et al. (1969)—auditory evoked response.
Bennett and Towse (1971)—Mental and psychomotor performance and finger tremor.
Bennett and Blenkarn (1974)—Multiplication—arithmetic and Wechsler-Bellevue Digit Symbol test.

In early tests of Behnke and Yarbrough (1939), inhalation of the totally unreactive gas, argon, inhaled with oxygen at a pressure of 10 ATA, brought about an even greater degree of stupefaction than inhalation of air at the same pressure. By contrast, inhalation of helium at even greater depths was devoid of untoward reactions (Behnke and Yarbrough 1938). End (1938) reported a diving descent to 420 ft with the diver inhaling a mixture of helium and oxygen (heliox). Currently simulated depths of over 2000 ft have been attained with inhalation of heliox to which some nitrogen is added to ameliorate effects of the High Pressure Nervous Syndrome (the trimix technique of Bennett) (Bennett et al., 1975).

Further work on breathing helium and oxygen (heliox) was reported by: Bennett and Towse (1971), and Bennett and Blenkarn (1974). Narcosis and the breathing of hydrogen was reported by Bjurstedt and Severin (1948) and Zetterstrom (1948). The anesthetic properties of breathing krypton was reported by Cullen and Gross (1951). Even oxygen is reported to have an anesthetic effect by Paton (1967), and by Bennett and Ackles (1970). From these empirical observations supported by quantitative test data, it could be concluded that elementary, monoatomic or molecular gases, devoid of chemical reactivity, could induce narcosis and even loss of consciousness. Carbon dioxide and cold increases the probability of nitrogen narcosis (Case and Haldane, 1941).

The term, narcosis, designates general depressant phenomena produced by drugs and gases. Anesthesia is a special instance of the general phenomenon characterized by loss of consciousness, altered cortical electrical activity, loss of pain sensation, and other signs familiar to the anesthetist. Narcosis is an apt term to denote many psychic reactions, including stupefaction and neuromuscular impairment associated with inhalation of inert gases under pressure, which may or may not be followed by loss of consciousness.

Narcotic potency of inert gases can be attributed solely to various physical properties, some of which may be enumerated:

Oil/water solubility (Meyer-Overton hypothesis);
Lipid or oil solubility (Meyer and Hopff, 1923; Carpenter, 1954);
Decrease in surface tension of monomolecular aqueous-lipid film (Bennett et al., 1967; Clements and Wilson, 1962; Bennett et al., 1975);
Thermodynamic activity (Brink and Posternak, 1948);
Polarizability and molecular volumes related to constants in van der Waal's equation (Wulf and Featherstone, 1957);
Increase in lipid volume with various ramifications of neural membranes to exceed a "critical volume" (Lever et al., 1971; Miller, 1977; Stern and Frisch, 1973).

Several other studies have served to elucidate the action of nitrogen in the production of narcosis: Meyer and Gottlieb-Billroth (1920) propounded the theory of narcosis; electroencephalographic changes induced by high partial pressure of nitrogen (Bennett and Glass, 1961); review of suggested causes of nitrogen narcosis was supplied by Hessler (1963).

Of particular interest is the pressure reversal of anesthesia (Lever et al., 1971); and the hydrostatic pressure reversal of narcosis in tadpoles (Johnson and Flagler, 1950).

In fact, extensive investigations during the past 25 years of inert gas narcosis to include narcotic effects of oxygen and carbon dioxide at elevated pressures have been not only highly stimulating but especially rewarding in revealing basic mechanisms underlying narcotic and anesthetic phenomena.

INERT GAS NARCOSIS

A. R. BEHNKE

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Särtryck ur Försvarsmedicin 1 : 31—37, 1965

Air breathing at 13 atmospheres. Psychological and physiological observations

John Adolfson and Anders Muren

Sammanfattning

Femton försökspersoner testades i tryckkammare under luftandning på 13 ata (motsv 120 m vattendjup). Flertalet försökspersoner var tränade dykare. Försök gjordes på 13, 10, 7 och 4 ata samt på 1 ata före och efter försöket. Dekompression företogs enligt specialtabeller. Manuell färdighet (bultbräda) minskade på 10 ooch 13 ata med 10 resp 35 %. Den aritmetiska räkneförmågan försämradesm ed 25 resp 62 %. Försök med fri association visade försämrade värden på 7, 10 och 13 ata med förlängd reaktionstid och minskade antal ord. De vanliga yttringarna av djupnarkos observerades på 10 ata med stora individuella variationer. På 13 ata förekom en rad symptom delvis av psykotisk karaktär med bl a minnesbortfall och syn- och hörselhallucinationer. Symptomen var snabbt övergående vid återgång till lägre tryckniva. En uttalad träningseffekt observerades med förbättrade prestationer vid upprepad exposition.

Pulsfrekvensen visade tendens till sänkning vid ökat tryck. Bestämningar av katekolaminer i urin visade inga påtagliga förändringar. En markant minskning av urinproduktionen förelåg vid tryck överstigande 4 ata. Det ökade luftmotståndet var subjektivt besvärande på 13 ata. Förändringen av talet var markant på 13 ata men det gick att uppfatta om försökspersonerna talade långsamt och distinkt.

Ett antal dekompressionssymptom förekom under eller efter dekompression, i vissa fall av tidigare icke beskriven karaktär. Alla behandlades på vanligt sätt utan kvarstående symptom.

Introduction

Diving with compressed air as a breathing medium has been practised since several hundred years. Among the different medical complications to diving, decompression sickness has probably been the most common reason for medical lesions and losses of lives among the divers. Since the introduction of modern deep diving, and especially during the last decades, depth narcosis, or the so called »nitrogen narcosis» has also cost a number of divers lives.

The reason for the depth narcosis is still obscure. Since the beginning of this century it has been observed and described by different authors (Hill & McLeod 1903, Hill & Greenwood 1906, Damant 1930, Case & Haldane 1941, Kiessling & Maag 1960, Adolfson 1965). According to these reports and to general experience among deep divers, the phenomenon appears at the level of 30—50 meters and the mental changes increases successively with increased depth until at a level of about 90 meters the diver is considered unable to take care of himself. At these depths the narcosis has much in common with alcohol intoxication. For the heavy divers the narcosis is seldom fatal. For the scuba divers (self contained underwater breathing apparatus) a pronounced depth narcosis often leads to drowning due to the fact that the diver tears off his breathing mouth piece or because of inconsiouness.

In the Swedish Navy as in the navies of most other countries using air as a breathing medium, 90 meters has been the depth limit for divers. In the US Navy and to a certain extent even in the British Navy diving to greater depths with helium/oxygen has been practised, although dives below 90 meters are only exceptionally made. (Behnke & Yarbrough 1939). The development of a method for routine diving to 150 meters is at present going on in the Swedish Navy. This method will, at least in the first stage, be based on helium/oxygen. Before this method is taken into practical use, however, it is considered desirably to attain an opinion on the utmost depth limit for air diving.

Methods

Fifteen experiments have been made in pressure chamber. In each experiment two persons were inside the chamber, the subject and the experimenter. Outside the chamber were one diving instructor and one naval doctor. The subjects were strictly volontary, naval personal, with few exceptiones experiensed divers. They were selected on ordinary medical grounds, age 23—47 years, and well informed about the possible risks involved. The experimenter was in all experiments either one of the authors or one of the two experiensed naval officers who were engaged in the investigation. [1] Both persons in the chamber were freely breathing chamber air (no mouth piece). For security reasons a television camera was installed in the chamber and was focused at the two persons whose reactions and expressions could thus be followed on the monitor outside. A film camera was as well placed in the chamber so that certain scenes could be recorded on 16 mm color film by remote control from the outside. All sound was continuously recorded during pressure exposition. The exposure time was usually 40 minutes, which caused a total decompression time of about 8 hours according to special tables worked out for these experiments.

A series of tests were made at different depth levels: 4, 7, 10 and 13 ata (corresponding to 30, 60, 90, 120 meters water depth). Two groups of investigations were made. In the first group of experiments manual dexterity and aritmetic calculation capacity were estimated on each depth level (for further details see. Adolfson 1965). In the other group of experiments a test of continous free association was made on each depth level. During this test the subject was presented a series of stimulus words at each pressure level and on each of these stimulus words he had to respond with a series of single words as rapidly as possible, during a period of 60 seconds. He was asked not to make an inventory of objects in the immediate surrounding; but to let each word that he mentioned freely suggest the next in order. An example would be »dog — cat — horse — buggy — wheel-tire — rubber — eraser — etc.» The associative reaction time and the number of responses given in 60 seconds were measured. The succession of depth levels was circulated so that in one experiment the succession was 4, 7, 10 and 13 ata; in the next experiment 13, 10, 7 and 4 ata. The same tests were made on surface level, i e at 1 ata before and after the actual experiment. All the responses were recorded on a tape recorder and the associative reaction time was measured in centiseconds.

The statistical signaficance of the observed differences was settled by analysing the differences between the results of the control tests and the tests at different pressure levels of the isolated individual (Ferguson 1959).

Heart rate was continuously recorded in most experiments, and electrocardiogram was taken in some cases on 13 ata. Estimations of adrenalin and noradrenalin in the urine were made on both subjects and investigators.

Apart from these variables the temperature of the chamber air was recorded during compression and decompression. All experiments except one were started in the morning at 8 to 9 o'clock a m after a light breakfast. During the decompression, usually at 12 o'clock at the 9—12 meters stop a meal consisting of 2 sandwishes and coffee or beer was served.

In some of the experiments decompression symptoms appeared, usually between the 6 and 12 meters stop. These were treated either by going back to next deeper stop or by breathing oxygen. Oxygen breathing was in some experiments intermittently instituted already at the 24 meters stop; more continuously for periods up to 1 hour from the 15 meters stop.

Results

Manual dexterity and arithmetic calculation

The results of the testing on manual dexterity and arithmetic calculation are described and discussed elsewhere (Adolfson 1965). From fig. 1 it can be seen that the capacity decreased with increasing pressure (from 88 % at the surface to 55 % at 13 ata for the manual dexterity and from 72 % at the surface to 10 % at 13 ata for the arithmetic calculation).

[1] Mr. G. Fahlman, Bureau of Ships and lt.cdr. P. Malmgren, Submarine Division, Naval Staff, R.Sw.N.

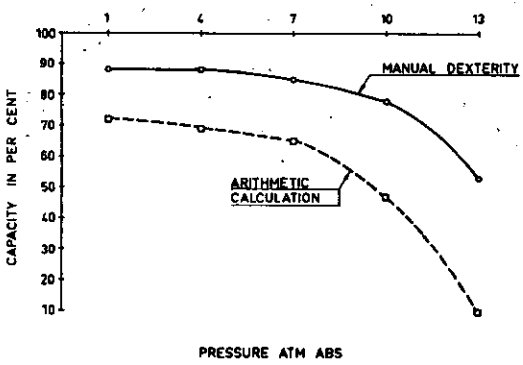

Fig. 1. Effects of hyperbaric air on manual dexterity and arithmetic calculation at rest.

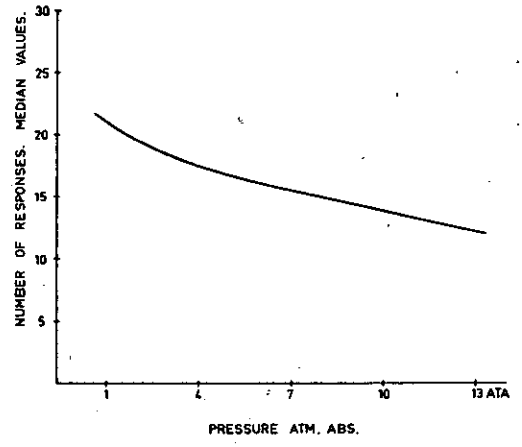

Fig. 2. Effects of hyperbaric air on associations. On the ordinate the number of responses per stimulus word.

Continuous free association

The stimulus words used can be seen in table I. The number of responses decreased with increased pressure. At 7, 10, and 13 ata the decrease was significantly different from the control values. Fig. 2 shows the median values of the number of responses per stimulus word on each pressure level.

The associative reaction time increased with increased pressure (fig. 3). At 7, 10 and 13 ata this increase was significantly different from the control values at 1 ata (surface).

Observations on general behaviour

At ambient pressures less than 10 ata the distrubances of mental and psychomotor functions were rather diffuse and uncertain. Only slight signs of mental disturbances could be observed. At 13 ata, however, mental disturbances were pronounced. Several subjects showed patterns of a psychotic type. There seemed to be no regular pattern of the symptoms, and it was difficult to establish a special order of their appearance or intensity. All the symptoms were readily reversible when the pressure was reduced. Some of the symptoms did, however, persist to 7 ata when going from 13 to 10 and to 7 ata; but they became obvious first at 13 ata when the succession of pressure levels was 1—4—7—10—13 ata.

The great majority of the subjects showed *alterations in mood and affectivity.* An euphoria or manic state developed in some cases: the subjects grew gradually excited when they tried to give a report of the situation inside the chamber. Their voices became more and more raised and

1 ata		4 ata		7 ata		10 ata		13 ata	
Sw	Eng	Sw	Eng	Sw	Eng	Sw	Eng	Sw	Eng
bal	ball	lus	louse	nisch	niche	trim	trim	smak	taste
rör	tube	lass	load	dikt	poem	skrock	superstition	kask	helmet
hål	hole	orm	snake	slagg	slag	skrubb	closet	best	beast
tre	three	tös	girl	hjon	servant	filt	blanket	halm	straw
bar	bar(-e)	alm	elm	nyck	faney	rytm	rhythm	lass	load
mast	mast	kaj	quay	rek	reg	rör	tube	muff	muff
frukt	fruit	kork	cork	stick	stick	rö	reed	sik	white fish
rem	strap	karm	rail	kol	coal	verk	work	trut	mug (gull)

Table I. Stimulus words.

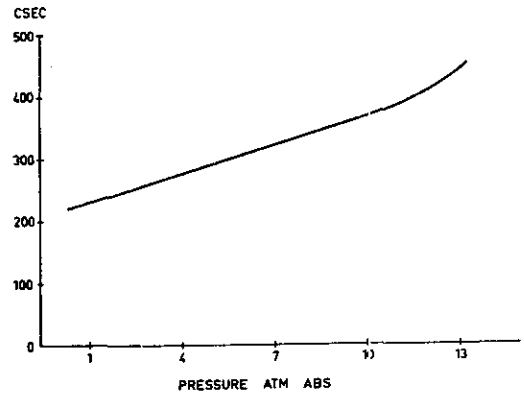

Fig. 3. Effects of hyperbaric air on associative reaction time. On the ordinate the median value in centiseconds per response.

finally they shouted observationes into the microphone. Other subjects became aggressive, irritable, insolent and fussy.

Alterations of consciousness were observed in most subjects. This impairment took different forms, from a general clouding of awareness of the surrounding with difficulties in concentration, to a definite sense of impending blackout. In one case there was a complete amnesia for the whole period at 13 ata, and at least two other subjects showed less pronounced, but still considerable memory disturbances. A disorganization of the perception of time could be observed in most cases. Some subjects belived that they had spent a few seconds at 13 ata, others several hours (the actual time period was 13—15 minutes).

Abnormal perceptional and psychosensorial phenomena were observed. Several subjects showed difficulties in conceiving and understanding given orders. They generally repeated the order, but did not obey it. They heard what had been said but they were not able to conceive or to carry out what they had been ordered to do. The

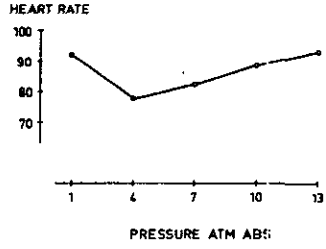

Fig. 4. Effects of hyperbaric air in heart rate at rest.

concentration upon the task required more energy than normally, according to the immediate reports given by most of the subjects.

A hallucinatory sensation of levitation — a feeling of lightness — was reported by one subject. »I feel as if the force of gravity is more or less removed, somewhat like I am in water». Not infrequently did the subjects experience a hallucinatory reverberation of auditory patterns, i.e. a spoken phrase or a melody heard once, was heard over and over again until it slowly faded away.

Changes in the visual figure background contrast was reported in two cases, and a general sense of increased intensity of vision and hearing was usually reported. Occasionally it could be observed how the subjects assumed an introspective attitude. They looked thoughtful and contemplative. One subject »was thinking and thinking during the test. The thoughts floated away».

The *motor reactions* were, as a rule, slower than normally and the motor disturbances reminded of the general clumsiness shown by a drunken person.

After a few exposures to 13 ata the subjects developed an obvius adaptation to the hyperbaric state. A convergence towards normal behaviour seemed to appear already after one or two exposures to 13 ata, partly due to a less pronounced change in the state of mind, partly to a concentration by an act of will or of selfdiscipline.

A recording of heart rate and electrocardiogram was introduced during these experiments, mainly for security reasons. Since the tests previously described were considered the most important ones, and since the pressure exposition periods had to be restricted in order to avoid very extensive decompression periods, the introduction and standardization of otherwise valuable tests had to be restricted. The electrocardiograms made on the subjects at 13 ata did not show any abnormalities in the cases it was recorded. Heart rate was recorded continuously in most cases, and as shown in fig. 4 there is a tendency towards a decreased rate during compression. With increase in pressure there is a return towards the control level.

Estimations of adrenalin and noradrenalin in the urine were made on both the experimenter and the subject inside the chamber. [1])

[1] The estimations were made at the Department of Physiology, Karolinska Institutet, by courtesy of professor U. S. von Euler.

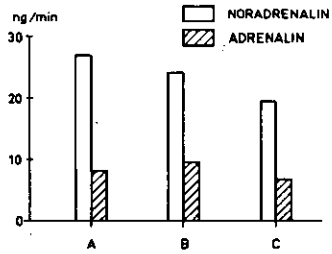

Fig. 5. Cathecholamines in urine in nanograms per min. A: Before the experiment (2—3 hours). B: During the experiment and first hour of decompression (2—3 hours). C: During decompression (6—7 hours).

As is obvious from figure 5 the values did not show any considerable changes during the actual experiment compared to the values obtained before and after (during decompression). A remarkable complication to this study appeared during the collection of urine samples. The intention was originally to obtain a sample from the actual pressure period, i e the first hour of the experiment. Practically all subjects, however, were unable to produce any urine during this period. Not until the pressure was lowered to the level of 3—4 ata a sample could be obtained. In some cases there was a period of complete anuria during more than two hours, after which half a litre was produced during fifteen minutes. At the beginning a temporary rentention of the bladder was suspected to be the reason. It became obvious, however, that the reason was a more or less complete interuption of the urine production in the kidneys.

The decompression was carried out according to special tables worked out for these experiments on the basis of the US Navy tables for 90 meter dives. The total decompression period varied between 7 and 9 hours depending on the exposition time (30—45 minutes). The safety limits were intentionally chosen as narrow as possible. This was made in order to check the reliability of the tables under well controlled conditions and strict medical supervision. In several cases light bends appeared, usually in the finger joints; but sometimes even in the elbows. These symptoms disappeared immediately when the pressure was raised again to next deeper stop, and after 10—15 minutes the decompression could be resumed according to the tables. Another effective procedure used in some experiments to avoid decompression symptoms was the introduction of pure oxygen breathing during the most critical stops (usually those between 15 and 3 metres). In some cases slight pain in the axillary regions with tenderness of the axillary lymph nodes was reported. In three cases a pronounced edema developed some hours after decompression; in one case in the right half of the face, in another on the upper part of both arms and in the third case on the back of the right hand. The swelling gradually disappeared during the next day.

The temperature within the chamber was increased up to 60° C during the rapid compression to 13 ata, and during the decompression from 13 to 10 ata and from 10 to 7 ata the temperature fell to about 10° C. The temperature fall gave rise to a dense fog due to the condensation of the air humidity. After some minutes at one pressure level, during which time the chamber was ventilated, the temperature usually stabilized to a level of about 25° C. The combined effect of high temperature and humidity, was somewhat disturbing during the tests, giving rise to pronounced sweating.

The well known change of the human voice due to the compression of the air was considerable at 13 ata. It was quite possible, however, to understand the speech at this pressure, at least when the subject made some effort to speak slowly and distinctly.

Another effect of the greatly increased density of the air at 13 ata, was the increase in breathing resistance. Some subjects complained about this effect, but a habituation to this condition seemed to occur. No estimations of the actual breathing resistance were made during this investigation.

Discussion and conclusions

The results of the present investigation confirm the well established fact that the higher the ambient pressure is, the more intense are the defects which can be measured in mental and psychomotor performance. The observations on the behaviour confirm the findings of an earlier investigation (Adolfson 1965).

In an attempt to verify the findings of Behnke, Thomson & Motley (1935) that the number of associative reactions decreased already at 4 ata, the investigation on continuous free association was performed. The value of an association

of this type can be discussed, and furthermore, Behnke et al. have not described their techniques. It is evident, however, that the number of associations decreases and the associative reaction time is prolonged with increased pressure. Behnke et al. and Kiessling & Maag (1960) showed that symptoms of deterioration appeared already at 4 ata. The discrepancy between their findings and the findings of this investigation could be due to differences in the technique and choise of subjects.

Many attempts have been made to classify word associations, but the responses are so various that no single classification has been generally accepted. But the number of responses and the associative reaction time can be used as an objective measurement of the associative connection. The quicker the reaction, the stronger is the associative connection. According to Woodworth & Schlossberg (1958) any stimulus word is capable of eliciting a number of different response words, though the subject usually makes only one single response. There must be some internal process of »inhibition» or »interference» which enable one response to block all others. Some of the subjects reported that two or more responses struggled for utterance, one getting in the others way, and most of the subjects reported periods of blankness in which nothing seemed to occur and no progress was made toward a response.

As for the physiologic mechanisms responsible for depth narcosis, nothing definite can be said at present. It seems obvious that it is intimately related to the breathing medium. There are three different gases who deserve consideration: nitrogen, oxygen and carbon dioxide. The old theory of nitrogen as the solely responsible gas in very doubtful. The fact that a gas with lower density as helium (Behnke & Yarbrough 1939) or hydrogen (Zetterström 1948) does not give rise to narcotic effects at corresponding pressures, and a gas with higher density as argon (Behnke & Yarbrough 1939) is more »narcotic» than air, indicates that breathing resistance is an important factor in this connexion. The important role played by carbon dioxide is apparent (Bean 1950, Bühlmann 1961).

A correlative study of the different manifestations of the depth narcosis and the changes of specific physologic and biochemical variables would seem to be the most fruitful approach to the elucidation of the phenomenon. Unfortunately this can hardly be made on the basis of the rather limited number of estimations of the last mentioned variables made in this investigation. There are, however, certain aspects of the present investigations who deserve further considerations.

The fall in heart rate when the pressure was raised was conspicuous in a number of cases. The existence in man of a »diving reflex» responsible for the redistribution of circulation in certain species in connexion with diving (Scholander 1940, Andersen 1963) can not be excluded. A more likely explanation, however, is the anxiety anticipation and exitation giving raise to increased heart rate prior to an experiment which may include certain risks or at least some discomfort. When the actual experiment has started, the subject relaxes and concentrates on his special task. The gradual increase in heart rate with further increase in pressure, is a natural consequense of augmented breathing work due to increased density of the air.

As for the cathecholamines in the urine samples, the relatively high »control values» (Fig 5 A) may also be explained by pre-experiment anixety. The values during pressure exposition were of the same order, whereas those during the decompression period were significantly lower. This could be due to a relative exhaustion of the sympathoadrenal system; but more likely to the fact that the subjects were both physically and mentally relaxed during decompression. They often assumed a recumbant position and sometimes went asleep for thort periods.

The inhibition of urine production during pressure exposition is somewhat difficult to explain. The pronounced sweating taking place during compression would cause a negative water balance with ensuing inhibition of urine production. This seemed not to be the whole explanation, however. Even when this fluid loss was compensated by the consumption of half a litre of water at the beginning of the experiment, practically no urine was produced until suddenly, at a pressure level arround 3 ata, large amounts were delivered. According to recent investigations (Gauer 1963), the degree of pressure or gas distension in the lungs has a considerable influence on reabsorption of water in the tubuli; the effect being mediated by nervous connexions from specific receptors in the lungs, influencing the production of antidiuretic hormone in the

pituitary gland. This mechanism may be operating even during pressure exposition.

Among the decompression symptoms, the cases with local edema were the most interesting. Similar symptoms have apparently been observed during deep diving experiments in the British navy recently (Mackay 1964). The distribution of the swelling and the tenderness of the lymph nodes indicates a local lymph stasis. A blockage by air embolism in the lymph nodes is possible. Another explanation could be a disturbance of capillary membrane permeability in certain regions, due to destructive action of microbubbles.

The investigation was supported by grants from The Delegation for Applied Medical Defence Research, Ministry of Defence, Stockholm.

The experiments were made at the Laboratory for naval medicine, Karolinska Institutet, Stockholm by courtesy of dr. C.-M. Hesser. Technical assistance was given by mr. J. B. Lundin and other members of the laboratory staff.

Special technical assistance on television and film technique was given by mr. Bengt Börjeson.

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IN: Am. J. Physiol. 1935; 112:554–558.

THE PSYCHOLOGIC EFFECTS FROM BREATHING AIR AT 4 ATMOSPHERES PRESSURE[1]

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Received for publication March 13, 1935

Air at high barometric pressures produces a narcotic effect on man. The changes which first appear at 3 atmospheres pressure are expressed in alterations of behavior, slowed mental activity, and impaired neuromuscular coördination. These effects, although previously observed, have not been attributed to the direct action of air or of the component gases, oxygen, nitrogen[3] and carbon dioxide.

Hill and Phillips (1932) reported that some of the deep sea divers (at depths of 270 to 300 feet, or 9 to 10 atmospheres absolute) had difficulty in assimilating facts and in making quick decisions, summarized as "a slowing of the process of cerebration." Severe emotional disturbances were sometimes observed and loss of consciousness reported. The men affected in this manner were regarded as psychologically unstable. Damant (1930) with reference to the paper of Hill and Phillips mentioned the "subtle change in character and behavior which comes over some men at less high air pressures," and considered that either the increased oxygen tension or impurities in the air might be responsible. Hill, according to Damant, excluded oxygen and carbon dioxide as etiologic factors.

Because of the many abnormal factors in the environment of the deep sea diver, the conclusion could not be drawn that changes in behavior and mental activity were caused by increased air pressure alone. It was of interest, therefore, to make observations on persons who were subjected to high air pressures in surroundings that were otherwise normal.

This paper presents a description of the psychic changes in air at 4 atmospheres, and the inference is drawn that the increased partial pressure of nitrogen is mainly responsible for the abnormal responses.

The observations were made in a large, well lighted pressure chamber described by Thomson, Yaglou and Van Woert (1932), on nine persons engaged in physiologic research under ordinary laborato-

The time of exposure to the increased pressure varied from 1.5 to 5 hours including decompression time. The temperature of the air was 25°C. and the relative humidity 50 per cent. Variations in temperature and humidity did not occur except for a period of 10 minutes during compression from 1 to 4 atmospheres and for a period of 2 minutes during decompression from 4 to 2.3 atmospheres.

The evaluation of the psychic changes was made on the basis of subjective and objective reactions of trained men engaged in animal experimentation. The usual procedures followed were cannulation of blood vessels, withdrawal of blood and cisternal fluid, collection of alveolar gas samples, and recording the blood pressure and oxygen consumption. Quantitative values have not been assigned to the changes, and their validity rests on the basis of a constant altered response of trained men when the air pressure was raised from 1 to 4 atmospheres.

OBSERVATIONS. The abnormal reactions were first felt at a pressure of 3 atmospheres. At 4 atmospheres the members of the entire group were affected in a similar manner with differences only in the degree of intensity of the responses.

Emotional reactions. As a pressure of 4 atmospheres was approached the individual was definitely aware of a feeling of stimulation, alertness and well-being—a definite euphoria. The mood was usually well controlled but occasionally expressed itself in laughter and loquacity. With a greater effort of self-control, normal conduct could be maintained.

Impairment of the higher mental processes. A slowing up of mental activity was a characteristic response. Visual, auditory, olfactory and tactile reception were not affected, but the response to these stimuli was delayed. A limitation of the power of association and a tendency toward fixation of ideas had to be counteracted. Recollection, consequently, required greater effort, and concentration was comparatively difficult. Frequent errors were made in arithmetical calculations and in the recording of data. One person had difficulty in telling time, confusing 43 minutes, for example, with 48 minutes. In the recording of time a reading of 12:15 might be written as 15:15. The responses were those of mild stupor in which greater effort and more time were necessary for accuracy.

Impairment in neuromuscular control. Increased difficulty attended the measurement of liquids and the manipulation of burettes and pipettes. The turning of stopcocks in the wrong direction was frequent. The impaired control of finer movements increased the breakage of glassware. The defect in coördination was essentially a past pointing or exaggeration of movement. The impairment, however, became negligible if slower movements were made.

In a single test at a pressure of 10 atmospheres (in another chamber) one member of the group felt a greatly increased numbness which amounted

to partial stupefaction. A simple task, the palpation of the pulse of another worker, was accomplished only with extreme difficulty. Efficient neuromuscular response was abolished.

That the changes increase in severity as the pressure is increased is shown by the responses at 3, 4, and 10 atmospheres. The retardment of mental activity is first felt at 3 atmospheres, becomes a slight handicap at 4 atmospheres, and at 10 atmospheres may render an individual helpless.

The altered responses occurred at the beginning of an exposure to increased pressure, and they did not change in intensity over periods of 3 hours. Irritability, fatigue and drowsiness were not present, but following decompression fatigue with a tendency to sleep was the usual reaction. Since this fatigue can be abolished by breathing oxygen during decompression, it is probably related to the presence of excess nitrogen possibly in the form of small bubbles.

DISCUSSION. *Nature of the changes.* The altered responses in air at high barometric pressures can be produced also by a variety of agents which depress the higher centers. Among these are alcohol, the inhalation anesthetics, i.e., ether, nitrous oxide, narcotic drugs, and conditions which lead to anoxemia. Thus the mental responses from decreased oxygen tension at normal barometric pressure (McFarland, 1932), and at moderately high altitude (Barcroft, 1925) are similar to the responses at increased air pressures.

Since the severity of the reactions is related to the degree of pressure and ranges from slight impairment at 4 atmospheres to partial stupefaction at 10 atmospheres, it is inferred that a limiting pressure incompatible with human activity would be reached between 10 and 15 atmospheres pressure.

The consideration of the etiology of the responses associated with high air pressures brings into the discussion the effects of the increased tensions of oxygen and nitrogen.

The action of the increased partial pressure of oxygen. At 4 atmospheres the partial pressure of oxygen in the air (4 × 21 per cent) is 84 per cent of 1 atmosphere, and at 10 atmospheres of air is equivalent to 2.1 atmospheres of pure oxygen. The breathing of pure oxygen, however, at pressures of 1 to 4 atmospheres does not induce the psychic responses of air with corresponding or considerably lower oxygen tensions (Behnke, Johnson, Poppen and Motley, 1935). Oxygen breathed for a period of several hours may disturb the coördination of finer movements, but euphoria is not present. In contrast with the effect of oxygen, the symptoms at high air pressures are immediate in their onset. The increased partial pressure of oxygen, therefore, cannot be a significant factor in the etiology of the changes.

The action of the increased partial pressure of nitrogen.[4] If oxygen is

[4] Includes argon and the rare gases.

excluded, then the atmospheric nitrogen can be considered as mainly responsible for the narcotic action of air at high pressures. Although nitrogen is chemically inert, the physical property which renders this gas analogous to narcotic substances is its high coefficient of solubility in lipoid matter. Ether and nitrous oxide which induce narcosis are also chemically inert substances. The Meyer-Overton law indicates that a definite relationship exists between the power of a narcotic (derivatives of the hydrocarbon series) and its "partition coefficient," or the ratio of the solubility in fat to the solubility in water. Although the Meyer-Overton law was formulated with regard to the aliphatic narcotics, it is not unreasonable to assume that the high concentration of molecular nitrogen in the lipoids of the central nervous system decreases cell membrane permeability to produce the changes characteristic of air at high pressures.

The "partition coefficient" of ether is 4.3, that of nitrous oxide 1.89, and that of nitrogen 5.0. Nitrous oxide induces anesthesia when the concentration in the blood is 0.017 mol per liter, and ether acts in the same manner when its concentration is 0.003 mol per liter. At an air pressure of 10 atmospheres the molal concentration of nitrogen in the blood is 0.0043, and at a pressure of 40 atmospheres 0.017 mol or the equivalent of the anesthetic concentration of nitrous oxide. While the limiting pressure at which air is respirable has not been determined, it is believed that loss of consciousness might occur between 10 and 15 atmospheres pressure.

PRACTICAL CONSIDERATIONS. An artificial gas mixture for divers is essential if operations at great depths (above 300 feet) are carried out, and for caisson workers if the exposure at and higher than 4 atmospheres be continued over long periods of time. Such a mixture, of course, should limit the oxygen concentration to that in the air at sea level, and in addition should provide a rapidly diffusible, sparingly soluble gas with a low "partition coefficient." The last qualification is of the greatest importance since large quantities of gas dissolved in fat relative to the amount dissolved in water increase the danger of bubble formation on decompression. Furthermore, if our hypothesis be correct, the psychic effects produced by a gas like nitrogen with its high solubility coefficient in fat, will be minimized.

SUMMARY AND CONCLUSIONS

Air at and higher than 3 atmospheres pressure exerts a narcotic effect on man with the characteristics of euphoria, retardment of the higher mental processes, and impaired neuromuscular coördination.

At 4 atmospheres these changes can be counteracted by increased effort, but at 10 atmospheres they amount to stupefaction with greatly impaired muscular activity.

The increased partial pressure of oxygen does not account for these changes. It is inferred that the atmospheric nitrogen is the etiologic

factor, and that it acts on the nervous system because of the high solubility coefficient of this gas in lipoid substances compared with that in water.

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U.S. NAVAL MEDICAL BULLETIN

XXXVI January 1938 No.1

PHYSIOLOGIC STUDIES OF HELIUM [1]

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INTRODUCTION

Twenty years ago the cost of helium [2] was of the order of $2,500 per cubic foot. Its present volume production at a cost of 1 cent per cubic foot has made it available for the flotation of airships, for use in medical treatment, and for the prevention and treatment of compressed-air illness.

In medicine Barach [3] began the study of the therapeutic use of helium particularly in the treatment of asthma and obstructive lesions of the larynx. More recently Eversole [4] tested its value in the field of inhalation anesthesia. The essential property making helium of value in these treatments is its decreased density compared with air.

In diving operations Sayers and Yant [5] suggested the breathing of helium because of its decreased solubility and more rapid diffusion rate. They showed that animals could be decompressed more rapidly

[1] From the Experimental Diving Unit, Navy Yard, Washington, D. C. Submitted for publication, July 18, 1938.

The authors desire to express their appreciation to Lieutenant Commander C. B. Momsen, United States Navy, for many valuable suggestions, and to members of the Bureau of Construction and Repair for the splendid support that they have given to these investigations.

The technical work of L. B. Lewis, pharmacist's mate, first class; T. Merritt, pharmacist's mate, first class; and H. H. Snider, pharmacist's mate; third class; was especially commendable.

[2] Information Circular about Helium. U. S. Bureau Mines Information Circular 6745, 1933.

[3] Barach, A. L. The Therapeutic Use of Helium. J. A. M. A., 107: 1273 (October 17, 1936).

[4] Eversole, U. H. Use of Helium in Anesthesia. J. A. M. A., 110: 878 (March 19, 1938).

[5] Sayers, R. R., and Yant, W. P. Value of Helium Oxygen Atmosphere in Diving and Caisson Operations. Anesth. and Anal., 5: 127 (June 1926).

in a He-O_2 atmosphere than in air. End [6] recently has experimented with helium in diving tests and his results are promising.

Some important properties of helium are its inactivity, since no compounds of helium are known to exist; its decreased density, one-seventh that of nitrogen; its rapid diffusion rate, twice that of nitrogen; and its extremely low liquefying temperature, —267.9° C., or about 5.2° C. above absolute zero. In the following series of physiologic studies additional facts will be presented as they developed during an investigation connected with the use of helium in diving tests in depths up to 500 feet carried out at this diving unit under the supervision of Lieutenant Commander Momsen, United States Navy.

I. RELEVANT OBSERVATIONS OF THE EFFECTS OF HELIUM ON THE HUMAN BODY

In the course of any extensive work with helium, investigators have invariably noticed several peculiar effects of this gas on the body. First among these effects is the change in voice. The laryngeal muscles controlling as they do the tension of the vocal cords are trained from childhood to produce different tones. This muscular training, however, is accomplished in an air medium, the density of which is considerably greater than that of helium. Therefore, when an individual is breathing helium and attempts to talk the muscles respond as they normally do in air. The resulting sound is higher in pitch and nasal in quality compared with sound emitted when air is breathed. It is interesting to note that divers who have repeatedly breathed helium mixtures have overcome these voice phenomena somewhat so that the voice tone approaches normal.

Second among the bodily effects is a certain degree of chilling during the exposure to helium mixtures. This chilling was more noticeable during suit diving when in the water, although a lesser degree occurred during simple breathing under pressure in a dry chamber. It was thought that this chilling possibly might affect the required decompression time by slowing the circulation particularly in the skin area. Measures have been taken to warm the body during helium breathing, but there has not been sufficient time or experimentation to determine the effect on gas uptake, or gas elimination, from the body.

With regard to bubble formation following exposure to high pressures it was reasonable to believe that gas emboli might form following helium breathing in a manner similar to their formation in an air atmosphere, if sufficient reduction in decompression time were made.

[6] End, E. Rapid Decompression Following Inhalation of Helium-Oxygen Mixtures Under Pressure. Amer. Jour. Physiol., 120: 712 (December 1937).

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This belief was substantiated by the occurrence of bends [7] while breathing or following the respiration of helium-oxygen mixtures. Certain differences, however, in the aspects of the cases of bends have been noted.

Preeminently there has been an absence of grave symptoms in a large number of cases. That is to say, symptoms such as unconsciousness and paralysis have not occurred. By contrast such mild symptoms as itching and skin rash have prevailed, frequently without sequellae. The occurrence of pain in about one-third of the cases has been promptly relieved by recompression and oxygen treatment.

To account for the absence of grave symptoms it should be noted that immediate treatment undoubtedly was an important factor, but, in addition, the low fat-water solubility ratio of helium compared with nitrogen is also an important consideration. Grave symptoms are usually produced when nervous tissue is the site of bubble formation. Such tissue having a high percentage of fat should absorb considerably less helium than nitrogen. Bearing in mind the low fat-water solubility ratio of helium, we have postulated further that in diving operations employing helium the important or controlling tissues concerned in decompression are those which are relatively rapid (tissues largely fluid) with regard to saturation or desaturation, whereas with nitrogen, the relatively slow or fatty tissues are all important. This theory gleaned from the laboratory has been one of the fundamentals in formulating decompression tables for use with helium.

In connection with the treatment of bends it has been frequently observed that the bends respond more quickly to recompression and usually require less pressure for relief of symptoms than is required for the treatment of nitrogen bends.

Of all the bodily effects of helium the most striking is the feeling of normality, in contrast with the usual intoxication and sense of pressure and depth associated with high air pressures. This improved mental condition of the diver has supplanted the saving in decompression time as the most important expected advantage in using helium.

II. SOLUBILITY OF HELIUM IN WATER AND OLIVE OIL COMPARED WITH NITROGEN

The body solvents for inhaled gases are hemoglobin, fluids, and fat. Determinations of the solubility of helium in fat are of importance, therefore, in estimating the time necessary for the body to come into equilibrium with a constant helium tension in the lungs.

[7] The term, "bends," usually refers to those symptoms of compressed-air illness characterized by pains in and around the joints. In this paper the term, "bends," will be used because of simplicity to include all symptoms (predominantly pain) arising from gas emboli, whether of helium or nitrogen origin, following decompression from high pressure atmospheres.

Since Campbell [8] has shown that the constituents of body fat, namely stearin, palmitin, and olein dissolve about the same amount of nitrogen per hundred cubic centimeters of substance as does bone marrow (90 percent fat), or about 5 cubic centimeters of nitrogen per 100 cubic centimeters when saturated with air at 38° C., and approximately 6.6 cubic centimeters when the nitrogen tension is corrected to 760 millimeters; determinations of the solubility of helium in olive oil containing about 72 percent olein and 28 percent palmitin should give an accurate estimate of the solubility of helium in body fat.

Experimental Method

Olive oil, U. S. P.[9], was equilibrated at a temperature of 38° by bubbling through the oil pure nitrogen or helium (97.65 percent) previously dried and freed from traces of carbon dioxide and oxygen by passage through sulphuric and pyrogallic acids for periods up to 1½ hours.

The inert gas was then extracted in vacuo by repeated shaking in the Van Slyke apparatus.

The solubility of helium and nitrogen in water was determined under the same conditions except that the respective gases were passed through water in place of sulphuric acid before admission to the tonometer tube. The type of analytic procedure employed in these determinations was similar to that developed by Van Slyke and his co-workers.[10]

Calculations

The volume percent of gas in the analyzed solutions was calculated by means of equations formulated by Van Slyke and Stadie [11] for reducing the pressure of a gas extracted in vacuo to standard conditions of temperature and pressure.

For water, the calculation simplified itself to—

$$\text{Vol. percent gas} = P \times N_2 \text{ factor}$$

For oil, i, the reabsorption coefficient, and α', the Ostwald distribution coefficient of a gas between gaseous and liquid phases, in the equation of Van Slyke and Stadie were omitted in the calculations since repeated gas extractions undoubtedly reduced these factors to a negligible minimum.

The helium in flasks was found by analysis to be 97.65 percent pure. The residual gas was assumed to be nitrogen, and the necessary corrections were made in the calculations.

Discussion of Experimental Results

The analytical data are enumerated in table 1. The solubility coefficient, α, represents the cubic centimeter of gas (0°, 760 mm.) dissolved per cubic centimeter of liquid.

In the water analyses the greatest difference between the highest and lowest values was 0.01 volumes percent, while in the oil analyses the greatest difference was 0.036 volumes percent.

[8] Campbell, J. A. and Hill, L. Quart. Journ. Exp. Physiol., 23: 197 (1933).
[9] Analyzed through the courtesy of Mr. Gault at the U. S. Naval Medial Center, Washington, D. C.
[10] Van Slyke, D. D., Dillon, R. T., and Margaria, R. Journ. Biol. Chem. 105: 571 (1934).
[11] Van Slyke, D. D., and Stadie, W. C. Journ. Biol. Chem. 56: 765 (1921).

Our solubility value for nitrogen in water is only slightly higher than the usually accepted value (0.01272),[10] while the value for helium in water is 0.022 volumes percent higher than the average reported by Hawkins and Shilling.[12]

The following solubility ratios have been computed from the values in table 1:

Helium/nitrogen in water	2 to 3
Helium/nitrogen in oil	1 to 4.5
$\frac{\text{Helium in oil}}{\text{Helium in water}}$	1.7 to 1
$\frac{\text{Nitrogen in oil}}{\text{Nitrogen in water}}$	5.24 to 1

It is observed that the oil/water solubility ratio for helium is only one-third of the corresponding value for nitrogen.

Fat/Blood Solubility Ratios for Helium and Nitrogen

The solubility of helium in blood [12] is about 1 percent higher than our value for the solubility of helium in water. Since the solubility of nitrogen in blood [10] is also 1 to 2 percent higher than the solubility of nitrogen in water, and since the solubility of the gases in oil is of the same degree as their respective solubility in body fat, it can be concluded that the fat/blood solubility ratio for helium is also only one-third of the corresponding ratio for nitrogen.

Application of Results

The comparatively low solubility of helium in fat is highly significant. Since fat and fatty tissue take up gas through the medium of the blood stream, this type of tissue governs the time required for the body as a whole to come into equilibrium with a given pulmonary gas tension.

With reference to nitrogen elimination from the body when oxygen is breathed, Behnke, Thomson, and Shaw [13] have pointed out that after the first hour the eliminated nitrogen comes mainly from fat and lipoid tissue. At the end of 6 hours nitrogen elimination had decreased to a value of about 7.5 cubic centimeters per hour. These measurements indicated that after 9 hours the body had lost 99 percent of its nitrogen content.

Campbell and Hill [14] using an entirely different method of determining tissue saturation concluded that 12 hours or more would be required for complete desaturation.

[12] Hawkins, J. A., and Shilling, C. W. Helium Solubility in Blood at Increased Pressures. Journ. Biol. Chem., 113: 649 (April, 1936).

[13] Behnke, A. R., Thomson, R. M., and Shaw, L. A. The Rate of Elimination of Dissolved Nitrogen in Man in Relation to the Fat and Water Content of the Body. Amer. Journ. Physiol., 114: 137 (December, 1935).

[14] Campbell, J. A., and Hill, L. J. Quart. J. Exper. Physiol., 23: 197 (1933).

On the basis of a blood/fat solubility ratio one-third that of nitrogen, helium should require from 3 to 5 hours for 99 percent elimination measured after the body had previously been in equilibrium with a given pulmonary tension of this gas.

The Helium Content of the Body

In a man weighing 60 kilograms the water content may be estimated at 70 percent or 42 kilograms, and the fat content at 13.2 percent or 7.92 kilograms. The helium content of the body at atmospheric pressure (helium tension in the lungs, 570 millimeters) may then be computed in the following manner:

	Cubic centimeters
0.00654 (a, H_2O, 570 mm.)×42,000	273
0.0111 (a, fat, 570 mm.)×8,800 (corr. for S. G.)	98
Body total	373

In a man weighing 60 kilograms the nitrogen content was found to be 840 cubic centimeters.[13] The helium content should be, therefore, about 45 percent as high as the nitrogen content of the body when the gas tension is the same in the lungs.

Possibility of Spinal Cord Injury Following Decompression From a Helium-Oxygen Atmosphere

Nitrogen emboli interrupting the blood supply to the thoracic and lumbar areas of the spinal cord produce the gravest complications of compressed-air illness, namely, paralysis affecting the lower extremities, intestines, and genito-urinary tract. Since the spinal cord consists of 27.5 percent fat,[13] a helium–oxygen mixture breathed in place of air should materially lessen damage to this vital tissue as a result of the comparatively low solubility coefficient of helium in fat.

SUMMARY

1. The solubility coefficients of helium in water and in oil have been determined and compared with the coefficients for nitrogen stand in the ratio of 2 to 3 for water and 1 to 4.5 for oil, respectively. From these values the helium content of the body should be about 45 percent as high as the nitrogen content when the same tension of each gas is breathed.

2. The decreased solubility of helium in fat compared with nitrogen should decrease the elimination time of this gas from the body and lessen the possibility of spinal cord injury.

TABLE 1.—*Helium, nitrogen solubility in water and in olive oil at 38° C*

Water		Olive oil	
α He	α N_2	α He	α N_2
0.00869	0.01274	0.01489	0.06689
0.00867	0.01269	0.01482	0.06653
0.00877	0.01273	0.01477	0.06668
0.00874	0.01283	0.01485	0.06669
		0.01467	0.06685
Average:			
0.00872	0.01275	0.0148	0.06673

III. MENTAL REACTIONS IN A HELIUM-OXYGEN ATMOSPHERE COMPARED WITH THOSE OCCURRING IN AIR

Behnke, Thompson, and Motley [15] first attributed the remarkable narcotic (intoxicating) effects of air at high pressures to the "atmospheric nitrogen." [16] It is worthy of note that although diving and caisson work had been in progress for a great many years, disturbances in motor control and behavior while occasionally recognized by alert diving officers (e. g. Saunders' report of the salvage of the *S-4*) were described in the literature for the first time by Hill and Phillips in 1932.[17]

In regard to the manner in which nitrogen affects these disturbances it has been pointed out [15] that its action might be related to its high solubility coefficient in fat compared with water. Thus, an analogy could be drawn comparing nitrogen with the aliphatic anesthetics, the activity of which according to the Meyer-Overton law appeared to be related to their ratio of solubility in fat compared with water.

The practical conclusion drawn from these observations [15] was summarized by stating that—

> An artificial gas mixture for divers is essential if operations at great depths (below 300 feet) are carried out * * * Such a mixture, of course, should limit the oxygen concentration to that in the air at sea level, and in addition should provide a rapidly diffusible, sparingly soluble gas with a low partition coefficient.

The gas contemplated was helium but its cost at that time (1935) did not render it available for large scale diving operations. Improved methods of application made its use more practicable and 3 years later an opportunity was afforded at this unit to substitute

[15] Behnke, A. R., Thompson, R. M., and Motley, E. P. The Psychologic Effects From Breathing Air at 4 Atmospheres Pressure. Amer. Journ. Physiol., 112: 554 (1935).

[16] Includes Argon.

[17] Hill, L. and Phillips, A. E. J. Roy. Nav. Med. Service, 18: 165 (1932).

a helium-oxygen atmosphere for air in depths up to 500 feet (16 atmospheres). It was possible, therefore, to test the belief that helium would free divers from the untoward effects of air,[6 15] and also to corroborate the finding that atmospheric nitrogen was responsible for these phenomena.

Essentially the helium-oxygen atmosphere abolishes, or renders negligible, the stupefaction and impaired motor control associated with air respiration under pressure. At a depth of 500 feet, for example, the diver felt well and was conscious of being at a depth of not more than 100 feet. The sensation of pressure or depth by which experienced divers breathing air can estimate to within 50 feet the actual depth is uniformly absent in a helium-oxygen atmosphere.

In contrast to the feeling of normality experienced in the helium atmosphere at deep depths is the complete change brought about by replacement of helium with air, the oxygen concentration remaining constant. The sudden introduction of air at a depth of 300 feet to a diver breathing helium produced a sensation of "floating away," dizziness, and loss of muscular control, accompanied by an insistent demand to be brought to the surface. In effect the diver was experiencing the first stage of inhalation anesthesia.

It would be of some value, perhaps, if arithmetical tests could be used to evaluate the reactions associated with the respiration of various gases under pressure. Such tests, however, are not practicable at the present time under our conditions of work. We have observed, for example, that arithmetical tests were of little value, since the effort and practice factors inherent in such tests rendered the interpretation of results difficult or invalid.

Since the air pressure disturbances are similar in many respects to those produced by alcohol, another narcotic substance, it seemed worth while to select a practical test of motor function from this carefully investigated field.[18] It appeared that typewriting involving as it does a complex, continuous skilled act, would give data indicative of the manner in which a diver would perform his tasks under pressure. In this test the continuous performance renders subjective reinforcement (possible in intermittent tests such as marksmanship) difficult, or detectable by a slower rate of typewriting. The practice factor can also be eliminated by using skilled typists as subjects.

These data were obtained when a skilled typist breathed air and a helium–oxygen mixture alternately at various pressures (depths) in a large steel chamber.

[18] Emerson, H. Alcohol and Man, p. 237. The MacMillen Co., New York, 1935.

	Air	He-O_2
Surface:		
Words per minute	63.2	69
Errors per stroke	0.0032	0.0052
200 feet:		
Words per minute	53.0	63
Errors per stroke	0.0135	0.005
250 feet:		
Words per minute	60.0	55.8
Errors per stroke	0.011	0.0057

Comparable to the alcohol tests[18] are the clumsy mistakes made in the copy (whole sentence omitted at 250 feet) greatly decreasing its legibility when air was breathed under pressure. Impaired judgment, a characteristic effect of high air pressure, is brought out by the fact that the typist realizing that he was making errors while breathing helium slowed down his rate of copy. Breathing air, on the other hand, gave him the feeling that he was doing exceptionally well and consequently he made no effort to decrease his speed.

Manner of Action of "Atmospheric Nitrogen" at High Pressures

The low partition coefficient (fat/water solubility ratio) of helium (1.7 to 1) in contrast with nitrogen (5.24 to 1), and the comparative freedom from pressure effects when helium is breathed, give us a working hypothesis toward an understanding of the action of nitrogen discussed in a previous paper[15]. While the nature of all narcotic activity is obscure, the relationship between narcotic potency of different alcohols and anesthetics and their relative fat and water solubilities as demonstrated by Meyer and Overton, may well apply to the narcotic action of gases. Specifically, an alteration brought about by adsorption or concentration of these fat solvent substances in the fatty components of the surface film of the nerve cell is thought to decrease cell membrane permeability with resulting narcotic effect.[18]

Other differences between the two gases (argon should also be considered with nitrogen and is included in the term, "atmospheric N_2") as an explanation of their opposite behavior may be related to the electronic inertness of the helium atom, depriving it of valence and the ability to combine with any known substance, in contrast with nitrogen which is electronically active, possesses valences of 3 and 5, and combines with many substances.

Limiting Depth When Helium Is Breathed

The limiting depth when air is breathed may be placed at 300 to 350 feet. If its narcotic action is related to its partition coefficient, then helium with only one third the partition coefficient of nitrogen should enable divers (considering only the mental effects) to descend to a depth of about 1,000 feet.

SUMMARY

In a helium–oxygen atmosphere the narcotic effects of "atmospheric nitrogen" at corresponding high pressures are largely dispelled. The comparatively low fat/water solubility ratio of helium compared with nitrogen suggests the applicability of the Meyer-Overton law toward an understanding of the nature of nitrogen narcosis.

IV. HELIUM CONTENT OF THE BODY AND ITS RATE OF ELIMINATION

Measurements of the rate of helium elimination from the body are essential for the calculation of decompression tables for divers.

Experimental Procedure

First-class divers representing carefully selected and trained men whose ages ranged usually between 25 and 35 breathed a helium-oxygen mixture for periods averaging 3½ hours either at atmospheric or increased barometric pressure. Following the period of helium respiration air or oxygen was rebreathed from a spirometer of the Benedict type. Analysis of spirometer gas for its helium content made possible the measurement of the body's helium content, and its rate of elimination.

Analysis of large samples of gas (500 cc.) enabled us to measure quantities of helium as small as 1.5 cubic centimeters eliminated from the body during a half-hour period of rebreathing, and to recover about 99 percent of the body's helium content. For our purpose we considered helium elimination complete when less than 1.5 cubic centimeters were given up by the body during a half-hour period.

The gas mixture breathed by the divers contained 73–76 percent helium, 5–7 percent nitrogen, and 19 to 20 percent oxygen.

Analysis of Helium

Helium can be separated from other inert gases by a physical method based on its low liquefying temperature. In the Cady apparatus activated charcoal is used to absorb nitrogen and gases other than helium at the temperature of liquid air (−189°). By means of a high vacuum applied to the charcoal the helium can be extracted, and subsequently measured in a burette.

A spectrum tube serves to identify helium, or impurities in the system, and to determine the approximate concentration of helium gas.

Computation of the Helium Tension in the Body

The helium tension in the body at the end of a 3½ hour helium-oxygen exposure was computed from the helium content of the urine instead of the helium percentage (73–76) of the inspired gas.

After 90 minutes of helium-oxygen respiration the tension of helium in the urine is in equilibrium with the helium tension of the kidneys, arterial blood, and alveolar gas (see part IV). By analyzing a sample of urine voided after 90 minutes for its helium content, and equilibrating a portion of the same urine

with pure helium, we can compute the tension of helium in the urine from the formula,

$$\text{Tension helium} = \frac{\text{helium content urine}}{\text{helium content equilibrated urine}} \times B - W$$

where B is the barometric pressure and W the tension of water vapor.

TABLE 2.—*Helium elimination from a diver, age 29, weight 74 kilograms (162 pounds)*

[The average initial helium tension in the body was 413 millimeters]

Time	Helium	Percent of total	Rate corresponds to a 50 percent [1] desaturation time in—	Time	Helium	Percent of total	Rate corresponds to a 50 percent [1] desaturation time in—
	Cubic centimeters		*Minutes*		*Cubic centimeters*		*Minutes*
3 minutes	75	29.0	6.25	180 minutes	247	94.6	43.00
20 minutes	147	56.5	17.00	210 minutes	251	96.2	43.00
30 minutes	169	64.8	20.00	240 minutes	254	97.3	43.00
60 minutes	201	77.00	27.50	270 minutes	256.5	98.3	43.00
90 minutes	223	85.4	31.00	300 minutes	258.5	99.4	43.00
120 minutes	233	89.3	36.00	330 minutes	260.0	99.5	43.00
150 minutes	242	92.7	40.00				

[1] A tissue half desaturating in 43 minutes will be 99.5 percent desaturated in 330 minutes (7.7 time units).

DISCUSSION OF RESULTS

The graph (fig. 15) represents the helium desaturation curve of a diver, age 29, weight 74 kilograms (162 pounds). The average helium tension in the body (urine) during the period of exposure in the helium–oxygen atmosphere was 413 millimeters.

In table 2 are listed the data applying to fig. 15. The helium given up during the first 3 minutes (lung-rinsing period) of oxygen breathing was estimated from values obtained for the third minute and from values computed from the product of cardiac output and the helium solubility coefficient in blood.

From these data we conclude that the quantity of helium dissolved in the tissues of men of the same weight is about 40 percent of the nitrogen content [13 19] for corresponding gas tensions in the body. The time required for helium elimination is about one-third to one-half the time required for nitrogen elimination.[13 14] The difficulty of measuring with precision the end point of nitrogen diffusion from the body in an oxygen atmosphere does not permit at this time a closer comparison of desaturation rate for the two gases.

The decreased total elimination time for helium as compared with nitrogen is roughly proportional to the blood and fat solubility ratios

[19] Behnke, A. R. Application of Measurements of Nitrogen Elimination to the Problem of Decompressing Divers. U. S. Nav. Med. Bul., 35: 219-240 (April 1937).

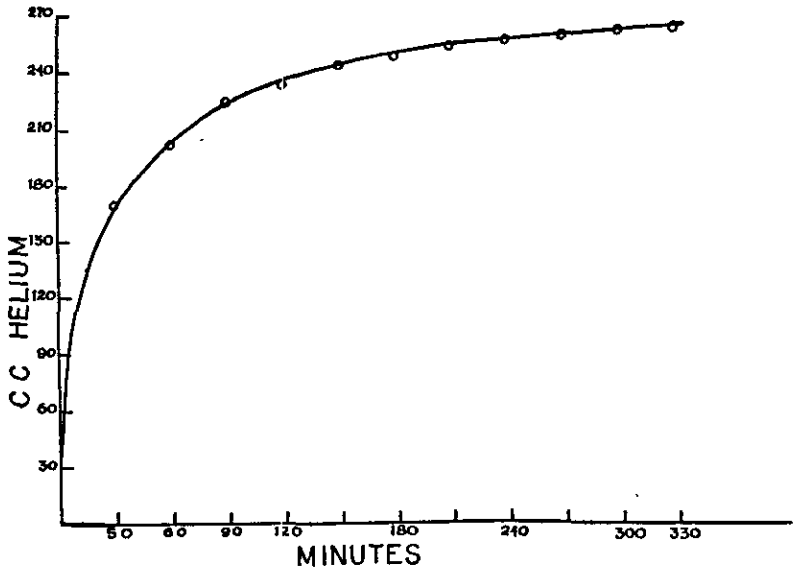

FIGURE 15.

of the two gases (viz. part II). Essentially it is the high solvent capacity of body fat for nitrogen that delays the elimination of this gas.[13] On the other hand, 50 percent desaturation time in contrast with total elimination time is about the same (20 minutes) for each gas. During this first 20-minute period gas elimination is taking place from body fluids.

POSSIBLE ERROR FROM THE ABSORPTION OF HELIUM IN THE INTESTINAL TRACT

The question may arise as to whether the small quantities of helium eliminated after fourth hour are given up by the tissues or alimentary tract.[20] Gas in the alimentary tract is mostly nitrogen, residual of swallowed air. When helium is breathed its entrance into the stomach and intestines occurs either by swallowing the gas or through diffusion from the blood stream. It is of interest to record that at one time experimental diving with helium was practically discontinued because the use of a mouthpiece for helium respiration resulted in swallowing large quantities of gas. During decompression the rapid expansion of the trapped gas caused intense, griping pains, and in addition created the possibility of gastric rupture.

To eliminate this source of error a test was conducted in which 500 cubic centimeters of helium were admitted to the small intestine

[20] McIver, M. A., Redfield, A. C., and Benedict, R. B. Amer. Journ. Physiol., 76: 108 (1926).

through a Rehfuss tube. A roentgenogram of the abdomen taken a half hour later revealed the gas distributed throughout the large bowel. Three and one-half hours later about 4.4 cubic centimeters of helium were recovered from air rebreathed in a spirometer during a half-hour period. While these quantities of gas would undoubtedly affect a precise determination of helium diffusion from tissues, it was doubtful whether or not such large quantities of gas would be normally retained. In a second experiment 200 cubic centimeters of helium were introduced into the small bowel. Between the fourth and fifth hour after the introduction of gas only 1.6 cubic centimeters were eliminated from the lungs.

These tests showed that under ordinary conditions helium either swallowed or diffusing into the intestinal tract during saturation will not introduce significant error in measurements of helium elimination.

SUMMARY

1. The helium content of the body is about 40 percent of the nitrogen content for corresponding gas tensions.

2. At atmospheric pressure 99 percent of the helium content is eliminated in five and one-half hours or in about one-half the time required for nitrogen desaturation.

V. THE NITROGEN OR HELIUM CONTENT OF THE URINE AS A TEST FOR BUBBLE FORMATION IN THE BLOOD STREAM

A simple test heretofore has not been available for estimating the efficiency of a given decompression schedule in promoting the elimination of excess gas from the tissues of the body without bubble formation.

Periodic measurements of the inert gas content of the urine provide a simple and effective test for detecting the presence of excess gas held in supersaturation or bubble form in the blood stream.

Leonard Hill [21] in 1907 made analyses of the gaseous nitrogen content of urine to determine the time necessary for kidney saturation. Subsequent investigators, however, have not continued Hill's work, nor have they applied the principle underlying the urine analysis method to the problem under consideration.

Method of Procedure

Urine from divers exposed to a helium-oxygen atmosphere under pressure and air during decompression, was collected before a dive (control sample), immediately after surfacing, and then at hourly

[21] Hill, L. Caisson Sickness, and the Physiology of Work in Compressed Air. Longmans, Green and Company, New York (1912).

intervals until equilibrium was again established between the inert gas tension in urine and lungs.

The manner of urine analysis was essentially the same as the technique used by Van Slyke and his coworkers in their nitrogen solubility studies.[10]

Since the solvent capacity of urine is decreased by the presence of dissolved salts it was necessary to equilibrate a portion of each sample by bubbling air through the urine for 15 minutes at a temperature of 38°.

The difference between the gas content of immediately analyzed urine and the equilibrated portion denoted gas held in supersaturation.

Principles Underlying the Experimental Results

A condition of equilibrium through the media of arterial blood and kidneys is assumed to exist between the inert gas tension in urine and lungs at constant barometric pressure. Disturbance of this equilibrium is effected when a diver is subjected to increased pressure by diffusion of gas from the lungs into arterial blood, kidneys, and urine. With the subsequent release of pressure, diffusion in the reverse direction occurs until equilibrium is again restored.

The time required for the reestablishment of inert gas equilibrium between urine and lungs will be delayed if gas bubbles are present in the blood, especially in the arterial blood circulating through the kidneys. That bubbles of gas circulate in arterial blood in the early stages of compressed air illness (bends) has been observed by Behnke and Shaw.[22]

In this paper experimental data will be presented in support of these statements.

Discussion of Experimental Results

Inert gas (nitrogen) content difference between bladder urine and equilibrated urine at atmospheric pressure.—In 76 analyses the inert gas content of bladder urine was found to average 0.015 volumes percent higher than the gas content of urine through which air was bubbled for 15 minutes. The greatest difference was 0.039 volumes percent. In 8 analyses the gas content of bladder urine was slightly lower (from 0.006 to 0.016 volumes percent) than the gas content of equilibrated urine.

Inert gas (nitrogen) content difference at increased pressure.—At 2.2 atmospheres pressure the same difference, or 0.015 volumes percent, was found to occur between bladder urine in equilibrium with lung air and urine equilibrated with air at the same pressure.

[22] Behnke, A. R., and Shaw, L. A. The Use of Oxygen in the Treatment of Compressed-Air Illness U. S. Nav. Med. Bul., 35: 61-73 (1937).

Barometric pressure changes in relation to equilibrium time.—Between 30 and 60 minutes was required for the establishment of equilibrium (saturation) between the pulmonary and urinary gas tensions when the barometric pressure was raised; that is, in a pressure chamber or diving suit.

When the excess pressure is lowered to normal the same time is required for the restoration of gaseous equilibrium (desaturation), provided that the excess pressure is not too high (above 7.5 pounds) or the return to normal too abrupt. Desaturation time is prolonged by rapid decompression from higher pressures. This delay is undoubtedly the result of increased nitrogen tension in the arterial blood reaching the kidneys and is possibly indicative of gas embolism.

Variation of inert gas content in the lungs in relation to the excess gas content in the urine.—In table 3, values are given for the excess inert gas in urine for periods up to 4 hours following the decompression of divers from a depth of 225 feet. On the bottom the divers breathed a helium-oxygen mixture and, during decompression, air. It is observed that the higher inert gas tension in the lungs is reflected in higher urinary gas contents.

Excess gas content in the urine in relation to bubble formation in the blood (bends).—In table 4, data are presented showing the relationship between the gas content of the urine and the occurrence of bends. The divers breathed a helium-oxygen mixture on the bottom and air during and following decompression. The control values in column 3 were obtained by analysis of urine voided immediately before a dive. Immediately following a dive the bladder was again emptied. The values in columns 1, 2, and 3 thus represented analyses of urine voided at the end of the first, second, and third hours, respectively. In these specimens, with one exception, helium could not be detected by our analytical methods.

We have come to regard the gas content values of the second hour (column 5) as of great importance since under the system of decompression employed, high values were associated with the development of bends while normal values (below 0.04 volumes percent) were obtained on divers who remained free from symptoms. In only one instance did bends occur following a normal 2-hour gas-content value.

On the other hand, high 2-hour values may not be followed by bends. Thus, diver Z. A. M., who up to date has been immune to bends, showed high values during the second and third hours. However M. A. C., who on the following day was subjected to the same diving conditions, developed severe bends.

Some factor apparently enables certain individuals to hold gas in supersaturation in the blood, or, if bubbles form, the blood flow, as a result of increased heart action or abundant collateral circulation, is sufficient to maintain adequate tissue nutrition. In this connection,

End [6] has called attention to the association of bends and the presence of high concentrations of carbon dioxide in caissons as reported in the literature. At this unit Lieutenant Commander Momsen has had an opportunity to make tests on two occasions in which a high carbon dioxide content in the diver's gas mixture was followed by the development of bends. In control tests duplicating the conditions of the previous dives except for a lowered carbon dioxide tension in the inhaled gas mixture, the divers remained in excellent condition.

That the body can tolerate gas bubbles in the blood stream is indicated by the inert gas values for the first and second hours obtained on B. U. G. This excess gas was found on analysis to be helium, the only instance in which we have been able to detect helium in the urine 1 hour after decompression and about 2½ after exposure in a helium-oxygen atmosphere. The existence of helium in bubble form in the blood is our only explanation for the prolonged presence of helium in the urine.

Further evidence of the presence of bubbles in blood associated with minor, and frequently prodromal symptoms of bends are brought out in tests involving a 2-minute return to normal pressure after a 30-minute exposure to a pressure of 4 atmospheres. Transient sequellae of such tests are skin itch and petechial rash indicative of bubbles in the cutaneous vessels. In explanation of this phenomenon it appears that gas in supersaturation is trapped in the skin vessels as a result of vasoconstriction brought about by the chilling cold associated with rapid decompression in a chamber. Subsequently, with an increasing differential pressure the gas in supersaturation is released in the form of bubbles.

Diffusion of helium through the bladder wall.—An important consideration in any study of urinary gas content is diffusion of gas through the bladder wall when the urinary gas tension is higher than the gas tension in the blood. During exposure in a high pressure helium-oxygen atmosphere the tension of helium in urine approaches equilibrium with the helium tension in the lungs. During decompression, however, the bladder urine loses about nine-tenths of its estimated helium content. This loss of helium undoubtedly takes place by diffusion through the bladder wall. The fugacity of helium is also greater in a distended bladder because, presumably, the stretched wall allows the gas to diffuse from urine more rapidly into the blood where the tension of helium is lower.

In an experiment designed to measure helium loss from retained bladder urine, 153 cubic centimeters of normal saline saturated with 1.63 volumes percent helium at two atmospheres pressure were introduced by catheter into the bladder. Three hours later the voided urine-saline mixture contained a helium content of only 0.07 volumes

percent. Making allowance for the dilution of saline by secreted urine, it was computed that nine-tenths of the original content of helium had diffused into the blood stream through the bladder wall.

SUMMARY

Periodic measurements of the inert gas content of the urine provide a simple and effective test for detecting the presence of excess gas held in supersaturation or in bubble form following the release of divers from high pressure atmospheres. By means of this test a quantitative estimate of gas elimination from the body can be obtained, and the occurrence of bends frequently can be prognosticated.

Data are presented indicating that helium diffuses through the bladder wall.

TABLE 3.—*The 225-foot dives, 20 minutes duration, diver breathing helium–oxygen mixture on the bottom*

Diver	Date	Excess inert gas in urine (volumes percent)				Oxygen percentage in helmet on bottom	Remarks
		1 hour	2 hours	3 hours	4 hours		
M. A. C.	Mar. 24	0.186	0.049	0.042	0.013	12.8	
	Mar. 25	.128	.035	.029	.013	21.1	
C. O. T.	Mar. 24	.266	.044	.031	----------	11.5	
	Mar. 23	.060	.009	.003	----------	20.6	
D. U. N.	Mar. 22	.134	.007	----------	----------	12.8	
	Mar. 24	.122	.002	----------	----------	22.9	
T. H. O.	Mar. 22	.132	.004	47-minute decompression		12.8	
	Mar. 25	.115	.020	42-minute decompression		21.7	
	Mar. 23	.105	.001	47-minute decompression		21.0	
M. E. T.	Mar. 28	.312	.044	.001	.01	9.8	
	Mar. 29	.104	.043	.009	----------	21.4	
F. O. R.	Mar. 23	.125	.031	.012	----------	12.0	
	Mar. 22	.110	.032	.021	----------	21.0	
F. R. Y.	Mar. 28	.149	.050	.001	.021	10.0	Itch,[1] rash,[1] fatigue.[1]

[1] Indicative of bubbles in blood vessels of skin.
[2] Frequent precursor of bends.

TABLE 4.—*Excess inert gas in urine in relation to the occurrence of bends*

Diver	Depth (feet)	Time on bottom (minutes)	Excess inert gas in urine (volumes percent)				Remarks
			Control	1 hour	2 hours	3 hours	
	(1)	(2)	(3)	(4)	(5)	(6)	
C. R. I.	350	20	0.018	0.11	0.05	0.017	Bends.
R. I. E.	350	20	.000	.05	.028	.017	No symptoms.
D. U. N.	400	20	.004	.099	.048	.041	Bends.
M. E. T.	400	20	----------	.13	.012	----------	No symptoms.
O. K. E.	400	18	----------	----------	.111	----------	Bends.
C. R. O.	400	18	.004	.18	.021	----------	No symptoms.
B. U. G.	375	20	.032	.20	.073	----------	Bends.
F. R. Y.	225	20	.029	.15	.05	.001	Mild bends.
M. E. T.	225	20	.015	.312	.044	.001	No symptoms.
B. U. G.	300	20	.009	[1].51	[1].35	----------	Cold during dive.
C. R. O.	350	20	.015	.14	.077	.005	Delayed bends.
Z. A. M.	350	20	----------	.17	.056	.051	No symptoms.
M. A. C.	350	20	----------	----------	----------	----------	Bends.

[1] Excess gas was helium.

IN: Am. J. Physiol. 1939; 126:409–415.

RESPIRATORY RESISTANCE, OIL-WATER SOLUBILITY, AND MENTAL EFFECTS OF ARGON, COMPARED WITH HELIUM AND NITROGEN[1]

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Received for publication March 21, 1939

In a previous paper by Behnke and Yarbrough (1938) it was pointed out that the remarkable stupefaction and neuromuscular impairment experienced by deep sea divers at depths below 100 feet could be eliminated or minimized by substituting helium for atmospheric nitrogen[2] in the divers' air supply.

The reactions characteristic of air intoxication or narcosis at high pressures are essentially slowed mental activity, inability to perform efficent manual work, and emotional disturbances which may culminate in loss of consciousness at depths below 350 feet (Behnke, Thomson and Motley, 1935).

Oxygen as an etiologic factor in these disturbances was eliminated by the demonstration that pure oxygen could be breathed at 4 atmospheres' pressure equivalent to the partial pressure of oxygen in air at a pressure of 20 atmospheres (corresponding to a diving depth of 630 feet) for periods of time up to 15 or 20 minutes without symptoms (Behnke, Johnson, Poppen and Motley, 1935).

In continuing our investigations it seemed advisable to ascertain the rôle played by argon in producing these mental phenomena, comprising as it does about 1.2 per cent of the atmospheric nitrogen.

In consideration of the importance of this problem in deep sea diving, in the treatment of respiratory obstruction, and in the study of the manner of action of the inhalation anesthetics, we have measured or described the breathing resistance, the oil-water solubility ratio of argon, and the mental impairment induced by breathing argon compared with helium and nitrogen.

1. *Respiratory Resistance of Argon Compared with a Mixture of Helium and Oxygen, and with Air. Method of procedure and experimental data.*

The subject 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.

[2] Includes argon and the rare gases.

Resistance to simulated vigorous respiration was tested by attaching a Benedict spirometer to a respiratory resistance machine[3] designed to determine resistance to breathing encountered in respiratory apparatus.

This appliance consists essentially of bellows controlled by a variable crank mechanism which could be operated at the rate of 15 inspiratory and expiratory cycles per minute. At this rate of speed approximately 32 liters of gas were admitted to the spirometer and the same quantity of gas withdrawn over a period of a minute. The resistance encountered in the to and fro passage of gas from bellows to spirometer was recorded by separate water manometers for each phase of the cycle. The smallest diameter in the circuit measured 0.75 inch at the junction of spirometer outlet and intake tube of resistance machine.

Successive measurements of resistance to gas flow were made with the spirometer filled with air, then with 80 per cent helium-20 per cent oxygen,

TABLE 1

Measurements of resistance to gas flow (cm. of water). Average of values for inspiration and expiration

PRESSURE	GAS TESTED		
	Air	80 per cent He 20 per cent O_2	86 per cent argon 14 per cent nitrogen
atms.			
1	3.25	2.15	3.65
2	4.60	2.85	5.05
3	6.10	4.05	6.95
4	7.50	4.95	8.20
Average.....	5.36	3.50	5.96

and finally with 80 per cent argon-14 per cent nitrogen. The results of these tests at pressures of 1 to 4 atmospheres are recorded in table 1.

Discussion of data. Under the conditions of our experiments the values for the machine tested resistance of the different gases were roughly proportional to the square roots of the gas mixture densities (specific gravities) if the density of air is taken as unity. As pointed out by Kernan and Barach (1937) Graham's law postulating that the rate of diffusion of a gas is inversely proportional to the square root of the density is applicable to the problem of breathing resistance of gases since it also governs the rate of effusion, or the passage of a gas through small orifices.

Barach (1936), in addition, found that the substitution of 80 per cent helium-20 per cent oxygen for air brought about a 30 to 50 per cent reduction in the pulmonary airway pressure of subjects breathing violently.

[3] Mine Safety Appliance Company, Pittsburgh.

Our results make an interesting comparison with Barach's data. The substitution of the helium-oxygen mixture for air decreased the pressure in the resistance machine 33 per cent, a value 9 per cent lower than the theoretical value calculated according to Graham's law. The argon mixture, on the other hand, increased the pressure 11 per cent compared with air, which is in agreement with the theoretical value.

Since the elevation of barometric pressure served to increase the density of the gas mixtures, at 4 atmospheres' pressure somewhat more than twice the resistance to gas flow developed compared with surface (1 atmosphere) values.

If Graham's law is also applicable at decreased barometric pressures, then the breathing of helium-oxygen at normal barometric pressure is equivalent insofar as respiratory resistance is concerned to breathing air at an altitude of about 18,000 feet (0.5 of an atmosphere).

With reference to actual respiration tests we could not detect any difference in resistance encountered in breathing helium-oxygen, air, or argon-oxygen at atmospheric pressure. At a pressure of 4 atmospheres there was also no appreciable subjective difference in respiratory resistance. The altered mental state, however, induced by atmospheric nitrogen when air was breathed, and by argon containing 20 per cent oxygen, was manifest at this pressure.

At a pressure of 10 atmospheres, equivalent to a diving depth of 300 feet, Lt. Comdr. Momsen, U. S. N., and one of the authors were able to breathe argon-oxygen for a few minutes only because of the increased resistance to breathing and the narcotic action of argon.

2. *Solubility of Argon in Olive Oil and in Water.* The solubility of argon in olive-oil was determined by bubbling an 86 per cent argon-14 per cent nitrogen mixture freed from water vapor, through the oil at a temperature of 38°C. for a period of one hour, and subsequently extracting the gases by repeated evacuation in a Van Slyke extraction chamber.

The solubility of the argon mixture in water was determined in a similar manner except that the gases were saturated with water vapor prior to passage through a tonometer tube.

Calculations were made from the equations formulated by Van Slyke and Stadie for reducing the pressure of a gas extracted in vacuo to standard conditions of temperature and pressure. A correction was made for the nitrogen present in the gas mixture.

In table 2 are listed the solubility values obtained compared with previously determined coefficients for helium and nitrogen (Behnke and Yarbrough, 1938). The solubility coefficient α, represents the cubic centimeters of gas (0°C., 760 mm.) dissolved per cubic centimeter of liquid.

3. *The Mental State Associated with Respiration in an Argon-Oxygen Atmosphere Compared with Air. Experimental procedure and results.* The

argon-oxygen mixture used in these tests contained 69 per cent argon, 11 per cent nitrogen, and 20 per cent oxygen.

At atmospheric pressure the argon-oxygen combination was breathed by experienced subjects through a mask attached to a spirometer. The results at this pressure were negative; the subjects were unable to detect any difference either in breathing resistance or in their mental state when argon, air, or helium were breathed successively.

For tests at increased pressures, divers dressed in regulation diving suits were placed in a 12-foot cylindrical steel tank containing about 8 feet of water. Increased depths were simulated by raising the air pressure above the water to any desired level. Observers on the outside of the tank maintained continual telephone communication with the divers who also could be observed through the glass ports in the walls of the chamber.

TABLE 2

Argon, helium, nitrogen solubility in water and in olive oil at 38°C., and the respective oil-water solubility ratios

WATER			OLIVE OIL		
α Argon	α Helium	α Nitrogen	α Argon	α Helium	α Nitrogen
0.0262	0.00872	0.01275	0.1395	0.0148	0.0667

Oil-water solubility ratios

ARGON	NITROGEN	HELIUM
5.32:1	5.24:1	1.7:1

The divers tested in these experiments represent carefully trained men of exceptional stability. Their experience in breathing air at pressures up to 10 atmospheres (300 feet diving depth) ranged from 5 to 20 years. As a result of this experience they have long been accustomed to the progressive stupefaction and neuromuscular impairment induced by air as the pressure is increased from 1 to 10 atmospheres. Moreover, the divers have become proficient in estimating their diving depth based on subjective reactions usually well within 50 feet of the actual depth.

Since the lives of the divers frequently depend upon their awareness to any change in the gas mixture breathed or in any unusual subjective reaction, they may be regarded with respect to the condition of their gaseous environment as sensitive and reliable indicators.

The tests were conducted in such manner that the divers did not know either their actual depth or the nature of the atmosphere breathed. They were asked to state their depth on the basis of previous experience in high

air-pressure environments. The results of these tests when argon was breathed are recorded in table 3.

These results indicate that argon induces greater stupefaction and neuromuscular impairment than air (nitrogen).

In addition one of the authors breathed argon under conditions similar to those prevailing for the divers, and experienced the usual altered mental state in a dive to a depth of 160 feet. The reactions, however, possibly as a result of subjective reinforcement, did not seem to differ greatly from those induced by breathing air at the same depth. Before the termination of the dive, the argon effect became strikingly apparent when, with the substitution of air for argon the mental fogginess cleared to such degree that the subject reported that he was being brought to the surface, unaware, of course, that a substitution of gases had been made in the atmosphere.

Discussion of results. Since argon comprises 0.94 per cent of the atmosphere, at a pressure of 10 atmospheres the partial pressure of argon would

TABLE 3

Estimates of diving depth made by divers breathing argon-oxygen based on their experience in breathing air at high pressures

DIVER	ACTUAL DEPTH	DEPTH FELT ACCORDING TO SUBJECTIVE REACTIONS
	feet	
1	130	200
2	90	150
3	130	200
4	120	250

correspond to that exerted by 10 per cent argon at atmospheric pressure. The failure of argon in a concentration of 69 per cent to affect experienced subjects at atmospheric pressure indicates that the small percentage of argon in air does not play a material rôle in nitrogen narcosis at high air pressures.

The argon effect, however, was apparent at pressure levels corresponding to depths from 90 to 300 feet. We can conclude that the depressant effect induced by breathing argon is greater than that experienced when air (nitrogen) is breathed. At the 300-foot depth the factor of increased respiratory resistance complicates the interpretation of subjective reactions, but at depths of 90 to 130 feet there can be no doubt that the mental responses are not greatly influenced by the respiratory resistance of argon. Of interest in this connection would be determinations of carbon dioxide elimination when argon, helium, and nitrogen are breathed under pressure.

These results are of interest in relation to the study of all gases inducing

narcosis. Helium, for example, elicits negligible mental aberrations compared with argon, while intermediate in its effect is the action of atmospheric nitrogen. To what properties of these gases may be attributed their different degrees of narcotic activity?

Argon like helium is chemically inert. There are no known compounds of these substances. Nitrogen, on the other hand, possesses valences of two and five and combines with many substances. Insofar as its narcotic activity is concerned it appears to be chemically inert since it can be almost completely recovered from the body when oxygen is breathed (Behnke, Thomson, and Shaw, 1935). Physical rather than chemical properties should therefore be considered in explanation of the action of these gases. In this respect they are comparable to lipoid soluble narcotics which are thought to act in a physical rather than a chemical manner.

Nitrogen and argon possess oil-water solubility ratios somewhat greater than the ratio for ether, and three times greater than the corresponding ratio for helium. This fact might account for the comparative freedom from untoward mental effects of individuals in a helium-oxygen atmosphere at high pressures. On the other hand, the greater depressant action of argon compared with nitrogen may indicate that the comparative solubility in oil of the two gases (argon being twice as soluble as nitrogen) enters into the problem. The foregoing facts are in accord with the Meyer-Overton law.

Another physical property that might influence the activity of the three gases is their molecular weight. As suggested by Lt. Comdr. Momsen, helium with a molecular weight of 4 induces the least disturbance, while the molecular weights of 28 and 40 for nitrogen and argon, respectively, indicate their relative difference in narcotic effect.

For the purpose of this paper it is sufficient merely to record that there are subjective differences induced by breathing argon or nitrogen compared with helium, and to enumerate the physical characteristics of oil-water solubility, and molecular weight as possible factors responsible for these differences.

SUMMARY

1. Simulated breathing resistance was tested in a respiratory resistance machine which admitted to and withdrew from a Benedict spirometer 32 liters of gas per minute.

2. The tested gas mixtures were: 86 per cent argon-14 per cent nitrogen, 76 per cent helium-4 per cent nitrogen-20 per cent oxygen, and air.

3. At pressures of 1 to 4 atmospheres the resistance to the passage of these gases to and from the spirometer varied as the square roots of their specific gravities (air = 1).

4. The oil-water solubility ratio for argon is 5.32 to 1 compared with a

value of 5.24 to 1 for nitrogen, and 1.7 to 1 for helium. Argon is twice as soluble, however, in water and in oil compared with nitrogen.

5. The narcotic effect of argon is greater than that of nitrogen at high pressures of 4 to 10 atmospheres, corresponding to depths of 100 to 300 feet.

6. At a pressure of 1 atmosphere no difference could be detected between argon, nitrogen, or helium with respect to respiratory resistance or psychologic effects.

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ABSTRACT

Bennett, P. B. and K. N. Ackles

The narcotic effects of hyperbaric oxygen.

In: Wada, J. and I. Takashi, eds. Proceedings of the fourth international congress on hyperbaric medicine, Sapporo, Japan, Sept. 1969. p. 74-79. Baltimore, Williams and Wilkins, 1970.

Five subjects were each exposed to 3 different pressures of oxygen and the amplitude of the averaged evoked responses together with arithmetic efficiency compared with that at atmospheric pressure. The results (Table I) indicate that hyperbaric oxygen will indeed depress the auditory evoked response without affecting arithmetic performance, except at 3 ATA O_2 (66 ft.) when the sums were significantly depressed (sums correct $P<0.05$, sums attempted $P<0.01$). However, at this pressure the evoked response is lower than at 2 ATA O_2 (33 ft.), where arithmetic efficiency appeared unaffected. This may be due to the small number of subjects studied or because of a balancing increase in excitability as one approaches pressures causing convulsions. It is relevant that Frankenhaeuser, Graff-Loggevig and Hesser using simple choice reaction times and mirror drawing found no significant impairment in 10 men exposed to oxygen at 3 ATA (66 ft.). More experiments are therefore required to verify the relationship between evoked response and arithmetic or other performance tests at 3 ATA. Nevertheless, hyperbaric oxygen does depress auditory responses in the brain without unduly affecting mental performance and this indicates a depression of the central nervous system by oxygen at pressures not sufficient to produce convulsions but enough to cause minimal narcosis. Before the narcosis is sufficient to materially depress performance, some other factor probably is affected by this gas which is very active, when compared with the inert gases. This factor is most probably enzyme inhibition. Wood has shown that the central inhibitory enzyme gamma-aminobutyric falls in the brain of animals exposed to hyperbaric oxygen and suggests convulsions are due to the decrease in its modulating action on nerve transmission. It is significant that unpublished data by Wood and the author did not show a similar fall in this enzyme in animals exposed to narcotic pressures of nitrogen and argon. (Authors)

ABSTRACT

Bennett, P.B., K. N. Ackles and V. J. Cripps.

Effects of hyperbaric nitrogen and oxygen on auditory evoked responses in man.

Aerospace Med. 40:521-525. 1969

The auditory evoked response (AER) is examined as a measure of narcosis induced at depth in diving personnel. Experimental AER data were obtained using electrodes attached to the scalps of experienced divers by computer averaging techniques. Auditory signals (clicks) at 60 dB were presented bi-aurally at a rate of 60 per minute for 1 min. or 5 min. An arithmetic performance test was given before and during compression to depths between the surface and 300 ft (10 ATA). The subjects breathed compressed air, O_2H and O_2H N mixtures. Compressed air caused decrements in both the AER and arithmetic efficiency which correlated with depth. Hyperbaric O_2 depressed the AER but did not affect arithmetic performance. Evidence is presented to show that N is the major cause of compressed air narcosis and that O_2 is not synergistic. It is concluded that the AER technique affords a reliable and reproducible measure of narcosis. The AER decrement with oxygen is discussed in relation to conduction deficiencies in the human brain and convulsions due to hyperbaric oxygen. (©B.A.)

JOURNAL OF APPLIED PHYSIOLOGY
Vol. 36, No. 1, January 1974. *Printed in U.S.A.*

Arterial blood gases in man during inert gas narcosis

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BENNETT, PETER B., AND G. DOUGLAS BLENKARN. *Arterial blood gases in man during inert gas narcosis.* J. Appl. Physiol. 36(1): 45–48. 1974.—To resolve the controversy whether compressed air narcosis is due to the raised nitrogen pressure or to hypercarbia because of respiratory embarrassment, four men alternately breathed air or heliox at 286 ft (9.6 Ata) and 190 ft (6.7 Ata) while measurements were made of Pa_{CO_2}, Pa_{O_2}, and pH in arterial blood from the radial artery. Between measurements, multiplication arithmetic and the Wechsler-Bellevue Digit Symbol test were administered which indicated, at 286 ft, decrements of 34.5% and 11.9%, respectively, when breathing air but no difference from controls when breathing heliox. At 190 ft the narcosis was less. All subjects, at both depths, with either gas, demonstrated hypocapnia, alkalosis, a positive base excess, and hyperoxemia. It is concluded that hypoxemia and hypercarbia are not the cause of compressed air narcosis, but that it is due to the raised nitrogen pressure. Counterdiffusion problems of urticaria and vertigo reported by others on changing from heliox to air were prevented successfully by prior addition of 25% nitrogen to the heliox.

compressed air intoxication and hypercarbia; mechanisms of anesthesia; counterdiffusion theory

AIR BREATHED AT DEPTHS in excess of 100–150 ft (4–5.5 Ata) causes signs and symptoms of narcosis characterized by euphoria, slowing of the higher mental processes, impaired neuromuscular coordination, overconfidence, hallucinations, memory loss, dizziness, and uncontrolled laughter and loquacity (6, 7). The narcosis becomes increasingly severe with increasing depth or pressure and at about 400 ft (13 Ata) loss of consciousness, aphasia, catalepsy, and personality changes may occur (1).

The cause of the narcosis is attributed generally to the raised nitrogen partial pressure (4) and its affinity for lipid in relation to the Meyer-Overton hypothesis (21, 23). Many other physiologically inert gases such as those of the noble gas series, helium, neon, argon, krypton, and xenon, also possess narcotic properties. Thus helium and neon are the least narcotic of the series and indeed there is supportive evidence that they are not narcotic (9, 10, 12). Xenon will induce surgical anesthesia at atmospheric pressure (22).

However, an alternative theory has caused controversy over recent years as to whether the narcosis is a function of the inert gas partial pressure or of hypercapnia and hypoxia as a result of increased airway resistance due to the increased density of the breathing gases (2, 3, 15, 27) and the associated expiratory effort causing subsegmental bronchial collapse (29).

An attempt was made to resolve this controversy during an experiment, known as Deep Work 1000, involving exposure of six subjects in a saturation oxygen-helium dive to 870 ft (27.3 Ata) with excursions to 1,000 ft (31 Ata) carried out at the F. G. Hall Hyperbaric Facility, Duke University Medical Center. Opportunity was taken during the decompression stages at 286 ft (9.6 Ata) and 190 ft (6.7 Ata) to measure arterial blood gases and performance efficiency while four of the men breathed alternately air or oxygen-helium.

METHODS

Changes of breathing mixture. Earlier studies which involved changing the breathing mixture from normoxic helium to normoxic nitrogen, while the body is in oxygen-helium, have resulted in severe cutaneous itching and urticaria (14) or an incapacitating vertigo when changing to oxygen-neon (20). In an attempt to mitigate this problem, it was decided to start adding nitrogen slowly at 526 ft (16.9 Ata) so that on reaching 382 ft (12.6 Ata) the mixture was composed of 75% He/25% N_2 and 0.45 Ata oxygen. The change from normoxic helium to air at 286 ft (9.6 Ata) and 190 ft (6.7 Ata) was therefore made with the body in this trimixture.

Experimental procedure. Decompression stages were made at 286 ft (9.6 Ata) and 190 ft (6.7 Ata) for 2.5 h and the tests were made at these depths.

Four of the six subjects in the pressure chamber were required to breathe compressed air for 30 min followed by the same period of time breathing 20/80 oxygen-helium. The gases were supplied from inside the chamber to a large-diameter plastic reservoir bag. From the bag three separate 2-inch hoses led to three oral-nasal masks fitted with low-resistance inlet and outlet valves. The expired gas was led to another large plastic bag and from there it was vented to outside the pressure chamber.

The performance tests used were multiplication of the two-figure by one-figure type (e.g., 98 × 6 = ?), the subject answering as many problems as possible in 1 min and the Wechsler-Bellevue Digit Symbol test, in which the individual is required in 1 min to relate symbols to a set of numbers from 1 to 9 given in a key.

The subjects were given these tests daily for a week prior to the dive and during the deep phases of the saturation

dive. This ensured that the subjects were on their learning plateau.

On reaching 286 ft (9.6 Ata) the blood gas equipment within the chamber was calibrated according to a methodology described previously (25).

During this calibration period one of the subjects breathed compressed air through a mask and was watched carefully to see if there were any symptoms or signs of vertigo or urticaria due to counterdiffusion.

After 30 min at 286 ft (9.6 Ata) the other three subjects started breathing compressed air. At 15 and 30 min after breathing air, arterial blood was withdrawn from each subject from an indwelling cannula in the radial artery and analyzed at once for P_{CO_2}, P_{O_2}, and pH. Performance tests were given in the interval between blood sampling and the subjects completed a questionnaire on their subjective sensations. The breathing mixture was then changed to 20/80 oxygen-helium and the sequence of blood sampling and performance testing repeated. The entire procedure was then repeated by the remaining subject.

After completion of the blood gas analysis, the decompression was continued and the test procedure repeated at the next 2.5-h stage at 190 ft (6.7 Ata) the following day.

RESULTS

No signs and symptoms of urticaria or vertigo were experienced by any of the subjects on making the change from oxygen-helium to air.

Subjectively, narcosis was noted breathing air at 286 ft (9.6 Ata) with numbness and tingling of the body, dizziness, reduced concentration and perception, analgesia (relief of discomfort secondary to a high-humidity-induced otitis externa) and a marked increase in the size of handwriting.

All the subjects reported that on changing from the chamber mixture to air at 286 ft (9.6 Ata) it was necessary to increase their rate of ventilation.

On changing to oxygen-helium, two subjects reported feeling more clear-headed, and two subjects noted little difference and did not know they were breathing oxygen-helium until they noticed their performance at the tests was better.

Performance tests and blood gas results obtained at 286 ft (9.6 Ata) and 190 ft (6.7 Ata) are shown in Tables 1 and 2, respectively. While blood gas measurements were not made during decompression prior to reaching 286 ft (9.6 Ata), measurements of performance were obtained when the subjects were breathing oxygen-helium prior to the addition of 25% nitrogen. These results are included as control measurements in Tables 1 and 2.

TABLE 1. *Mean results of human mental performance and arterial carbon dioxide in air and 20/80 oxygen-helium at 286 ft (9.6 Ata)*

Test	Control	20/80 He/O_2	Air 20/80 N_2/O_2
Arithmetic correct	16.8 ± 1.78	16.33 ± 2.08	11.00 ± 1.73
Wechsler-Bellevue	50.5 ± 5.61	51.50 ± 5.88	44.50 ± 1.21
Pa_{CO_2}/15 min		31.13 ± 2.78	34.83 ± 3.05
Pa_{CO_2}/30 min		35.38 ± 4.36	34.73 ± 3.84
pH/15 min		7.52 ± 0.02	7.52 ± 0.01
pH/30 min		7.50 ± 0.03	7.50 ± 0.02
Base excess 15 min		3.0 ± 0.91	3.6 ± 1.55
Base excess 30 min		3.38 ± 1.25	4.75 ± 1.26
Pa_{O_2} 15 & 30 min		1,033.75 ± 144.3	1,100.29 ± 73.68

Values are means ± 1 SD.

TABLE 2. *Mean results of human mental performance and arterial carbon dioxide in air and 20/80 oxygen-helium at 190 ft (6.7 Ata)*

Test	Control	20/80 He/O_2	Air 20/80 N_2/O_2
Arithmetic correct	16.8 ± 1.78	18.67 ± 1.53	15.67 ± 2.08
Wechsler-Bellevue	50.5 ± 5.61	50.00 ± 5.42	51.20 ± 4.19
Pa_{CO_2}/15 min		35.13 ± 2.84	34.60 ± 1.99
Pa_{CO_2}/30 min		35.05 ± 2.56	32.68 ± 1.60
pH/15 min		7.49 ± 0.03	7.50 ± 0.03
pH/30 min		7.50 ± 0.03	7.51 ± 0.01
Base excess 15 min		4.00 ± 0.91	4.50 ± 1.30
Base excess 30 min		4.38 ± 0.48	5.00 ± 0.82
Pa_{O_2} 15 & 30 min		634.00 ± 93.21	702.88 ± 133.59

Values are means ± 1 SD.

Compared with control data, the arithmetic test at 286 ft (9.6 Ata) when the subjects were breathing air, indicates a significant decrement of 34.5% ($t < 0.02$) and the Wechsler-Bellevue Digit Symbol test, a decrement of 11.9% ($t < 0.05$). The values while breathing 20/80 oxygen-helium are, however, no different from the control values.

The Pa_{CO_2} values indicate no significant difference when breathing air or oxygen-helium at 286 ft (9.6 Ata) or 190 ft (6.7 Ata). All subjects demonstrated hypocapnia, alkalosis and a positive base excess. In no instance was hypercapnia observed in arterial blood.

The Pa_{O_2} results in Tables 1 and 2 are shown as means for the results of the 15- and 30-min measurements and indicate the presence of the high values anticipated for the administered pressure of oxygen.

DISCUSSION

Narcosis and blood gases. A number of workers have proposed hypercapnia and/or hypoxia as possible causes for the narcosis found in men and animals breathing compressed air. Bean (2) reported acidosis in dogs during compression with reversal during decompression, which was attributed to an interference with removal of carbon dioxide. This was considered due to compression-induced inflow of gases into the lungs during rapid compression, together with increased airway resistance due to the increased density of the breathing gases.

Rashbass (24) measured alveolar carbon dioxide in 26 men compressed with air to 250 ft (8.6 Ata) and correlated the results with performance efficiency. These results, however, failed to support the carbon dioxide theory as did similar experiments by Cabarrou (17).

Nevertheless a little later Seusing and Drube (27) and Buhlmann (15) again denied that nitrogen or the inert gases were narcotic and reiterated that the narcosis was due to carbon dioxide intoxication.

Conversely Bennett (5) made measurements of tissue carbon dioxide and oxygen tension from glass electrodes resting on the cortex of chloralosed cats, using auditory induced evoked potentials to quantify the degree of narcosis, and found no correlation between the carbon dioxide tensions and the narcosis present.

Hesser, Adolfson, and Fagreus (19) analyzed the effects of

nitrogen and carbon dioxide in a study exposing men to a variety of carbon dioxide partial pressures in air at 165 ft (6 Ata), while measurements were made of alveolar carbon dioxide and performance efficiency. The results indicated the carbon dioxide component to be negligible at alveolar tensions below 40 mmHg and that high alveolar nitrogen and carbon dioxide pressures are additive in their effects on performance. Further, when the nitrogen and carbon dioxide tensions are raised simultaneously, the effect is greater than the sum of the changes induced by the two gases separately.

However, more recently, Vail (29) has reiterated that nitrogen narcosis is a myth and suggests rather that the cause is the molecular density of the breathing mixture associated with expiratory effort causing subsegmental bronchial collapse, which results in hypoxia and carbon dioxide retention. The increased density, together with the extra-expiratory effort, generates, it is suggested, transpulmonary pressures in excess of maximum transpulmonary pressure which causes collapse of the subsegmental bronchi with a blocking of gas exchange from alveoli.

The present experiment induced in all subjects an acute respiratory alkalosis, the magnitude of which was identical with both air and oxygen-helium and was identical at both 286 ft (9.6 Ata) and 190 ft (6.7 Ata). However, all subjects demonstrated also a small mean positive base excess of 4.1 ± 1.1 meq/l (standard bicarbonate 27.7 meq) which may be interpreted as the chronic metabolic adaptation to a mild hypercapnia of 44–50 mmHg under the steady-state conditions pertaining to the saturation part of the dive.

This mild degree of hypercapnia corresponds to steady-state measurements of blood gases made by Saltzman et al. (25) in three men at 200 ft (7.05 Ata) and 250 ft (8.57 Ata) breathing alternately normoxic oxygen-nitrogen, normoxic oxygen-helium, and normoxic oxygen-neon. These results indicated that at 7.05 Ata (200 ft) the Pa_{CO_2} with the helium was 45.5 ± 2.02 mmHg and for nitrogen was 45.0 ± 1.75 mmHg, compared with 41.1 ± 0.91 on the surface breathing air. Simultaneous measurements of the electroencephalogram (EEG) and visual reaction time (28) indicated a suggestion of an increase in the mean alpha frequency, a linear increase in reaction time and an increase in failures to respond during the reaction time test when subjects breathed oxygen-nitrogen. The oxygen-helium mixture had no effect. The small increase in carbon dioxide tension was related to the pressure rather than density. The increase was the same for both nitrogen and helium, whereas there was an indication of narcosis only with the nitrogen mixture during the reaction time test. This suggests that the raised arterial carbon dioxide is not responsible for the narcosis. The presence then of a small base excess or an increased standard bicarbonate is corroborative of previous work which suggests that hydrostatic pressure results, in some yet to be defined manner, in mild hypoventilation and mild hypercarbia (25). As these studies were carried out during a decompression stage, the creation of a respiratory steady state was not possible and the subjects mildly hyperventilated.

The present results confirm the finding that there is no significant difference in the arterial carbon dioxide values whether oxygen-helium or oxygen-nitrogen are breathed. However, narcosis was definitely present with the latter. The reduction of 34.5% with the arithmetic test in air compares with a decrement of 30 ± 5.3% in earlier studies (8) in men breathing air at 300 ft (10 Ata) and the less sensitive Wechsler-Bellevue Digit Symbol test decrement of 11.9% compares with a mean decrease of 6.6% for men at 220 ft (7.6 Ata) compressed air (11).

The present experiment minimized the requirement for carbon dioxide elimination. All subjects were at rest breathing through equipment of minimal dead space and resistance and all inspired gas was completely devoid of carbon dioxide. Under less favorable conditions of diving and work, both carbon dioxide production and work of breathing may well be increased severalfold and inspired gas might contain significant amounts of carbon dioxide. Under such circumstances hypoventilation might occur leading to hypercarbia and potentiate any coexistent inert gas narcosis.

The degree of hyperoxemia observed is consistent with the high inspired tension of oxygen and rules out any significant impairment of oxygen transport across the lung. That the Pa_{O_2} values are a little lower than might be expected is probably due to small leaks in the reservoir bag or the oral-nasal masks.

Thus the contention of airway collapse causing hypoxemia and hypercapnia resulting in signs and symptoms of narcosis (29) is not confirmed by direct experimental measurement under conditions in which marked narcosis was evident by both subjective and objective criteria and the narcotic property of nitrogen at raised pressures is substantiated.

Counterdiffusion. There have been several diving experiments in which either a severe cutaneous itching and urticaria or an incapacitating vertigo occurred while changing the breathing mixture from normoxic helium to another inert gas (14, 20).

Conversely, breathing oxygen-argon in air had no effect (13). Neither did substituting compressed air at 200 ft (7.05 Ata) for oxygen-helium during a decompression from 1,000 ft (31 Ata) in other deep dives (16, 26).

In the two conditions where problems occurred, the change was made from pure oxygen-helium to oxygen-nitrogen or oxygen-neon, whereas in the uneventful exposures a proportion of nitrogen was present in the breathing mixture prior to the change.

That no vestibular or cutaneous lesions occurred in the present experiment when changing to air from chamber gas, is attributed, therefore, to the addition, prior to the change, of the 25% nitrogen to the oxygen-helium. Support for this in relation to the counterdiffusion theory for origin of the lesions was obtained from a modification of the Graves et al. (18) formula to determine the ΔP at the interface. The earlier 250-ft dive at Duke University gave a ΔP of 45 ft for the change made at 200 ft (7.05 Ata) which is more than sufficient to generate bubbles. Had the change in the present study been made at 286 ft (9.6 Ata), without prior addition of nitrogen, then the ΔP would have been 27 ft, which is borderline for bubble generation. The addition of the 25% nitrogen reduced the ΔP to 15.5 ft, which would not be expected to cause bubbles and indeed, apparently did not.

Here then may be a practical solution to the counter-diffusion problem. In fact, addition of the nitrogen to oxygen-helium well before the change in breathing gas, as in the present experiment, may be advisable in many decompressions where air is employed from 150 ft to the surface. Although the ΔP at this depth on making the change may not be sufficient to generate bubbles, if the decompression profile is ineffective and "silent" bubbles have been formed, the ΔP may be sufficient to permit the bubbles to attain a critical size so that decompression sickness is caused.

The invaluable contributions of all participants in the experimental simulated dive January 20–February 2, 1973, is gratefully acknowledged; in particular that of the subjects Goeff Baker and "Dutch" Ritter of Oceaneering International and Chuck Meyer and John Atwell of the Harbor Branch Foundation and the National Oceanic and Atmospheric Agency, respectively. The technical assistance with blood analyses while at pressure of Mr. Butch Doar is gratefully acknowledged.

We are grateful to Dr. E. Flynn, University of Buffalo for the calculations in relation to the counter diffusion theory and to Dr. H. A. Saltzman for his advice.

The work was supported in part by grants from the National Heart and Lung Institute (HE-07896), the Harbor Branch Foundation, Oceaneering International, and the Office of Naval Research Contract N00014-67-A-0251-0022 with funds provided by the Naval Bureau of Medicine and Surgery.

Received for publication 16 April 1973.

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ELECTROENCEPHALOGRAPHIC AND OTHER CHANGES INDUCED BY HIGH PARTIAL PRESSURES OF NITROGEN.

P. B. Bennett and A. Glass

SUMMARY

Men have been subjected to compressed air in a pressure chamber and their electroencephalograms recorded while they solved arithmetical problems. At atmospheric pressure these problems elicited a blocking of the alpha rhythm, but after a variable time at increased pressures no such alpha blocking occurred. The time from the beginning of their exposure to high pressures, until abolition of the alpha blocking response, was found to be inversely proportional to the square of the pressure, i.e. $P\sqrt{T}$ is a constant. If after blocking abolition, an oxy-helium mixture was substituted for the compressed air, blocking reappeared, implicating nitrogen as the agent responsible.

A diminution in the amplitude of the alpha activity was observed at 7 atm absolute which was severe at 10 atm absolute. At these pressures, when the time to abolition of blocking was very short signs and symptoms of narcosis were present. Correlations between the EEG findings and the mental state are discussed, together with their possible connection with the ascending reticular formation of the brain stem.

ABSTRACT

Bennett, P. B., D. Papahadjopoulos, and A. D. Bangham.

The effect of raised pressure of inert gases on phospholipid membranes.

Life Sciences 6:2527-2533, 1967.

Euphoria and narcosis occur when man breathes inert gases (nitrogen, argon, neon, helium) under increased atmospheric pressure. Among the many mechanisms suggested for this action were inhibition of cell metabolism, blocking of carion permeability, or inhibition of the sodium extrusion pump. It was shown that there was an electrolytic imbalance with a fall in extracellular sodium and chloride ion concentration during narcosis. The present study examined the reason for this imbalance and demonstrated quantitatively that it was related to the presence of inert gas in the lipid membrane. That is, breathing nitrogen caused a linear increase in the lipid monolayer pressure as the gas phase pressure increased. At the pressures used helium did not appear to swell the monolayer and this would cause no narcotic effect.

VOLUME 42
NUMBER 11
NOVEMBER, 1971

Aerospace Medicine

FORMERLY THE JOURNAL OF AVIATION MEDICINE
FOUNDED BY LOUIS H. BAUER, M.D.
Official Publication of the Aerospace Medical Association

Performance Efficiency of Men Breathing Oxygen-Helium at Depths Between 100 feet and 1500 feet

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BENNETT, P. B., and E. J. TOWSE. *Performance Efficiency of Men Breathing Oxygen-Helium at Depths Between 100 feet and 1500 feet.* Aerospace Med. 42 (11): 1147-1156; 1971.

Experiments are described in which two subjects were compressed at 16-17 ft/min with 0.45 ats abs oxygen and helium to 100 ft/24 hrs, 300 ft/24hrs and 450 ft/24 hrs culminating in a stage compression through 600 ft/24 hrs, 1,000 ft/24 hrs, 1,300 ft/24 hrs to 10 hrs at 1,500 ft.

Measurements were made of mental and psychomotor performance, finger tremor and personal comments. The results indicate no mental deterioration at depths as great as 1,500 ft but a decrement in psychomotor performance due to the presence of tremors. Susceptibility to tremors varied significantly, one of the subjects being unaffected whilst the other showed an increasing postural tremor with depth which was enhanced by each compression phase. These findings are discussed in connection with the effects of rate of compression, introduction of 24-hr stages in compression to great depths, EEG changes and the appearance of sensations of impending loss of consciousness and somnolence (microsleep). It is concluded that helium does not induce an inert gas narcosis similar to that of nitrogen or argon and that the increased tremor and psychomotor decrement, as facets of a High Pressure Nervous Syndrome, are due to the action of pressure per se.

IN ORDER TO CIRCUMVENT the problem of compressed air narcosis[4] at depths greater than about 200 ft, the inert gas helium usually is substituted for the nitrogen constituent of air. This has been so since the late thirties[1,16] and its use has radically increased with the advent of saturation diving.[15,20]

The narcotic potency of an inert gas may be related to many of its physical constants[10] but lipid solubility gives one of the best correlations. On this basis, signs and symptoms of narcosis would be expected breathing helium at about 800 ft and to be as severe as those with air at 300 ft when breathing oxygen-helium at about 1,350 ft. Alternatively, Carpenter[14] inferred on the basis of rat experiments that helium may not be narcotic even at 1,500 ft, provided that the attending hydrostatic pressure is of no consequence. Further, as a result of *in vitro* studies on the penetration of a lipid monolayer by various inert gases in connection with studies of the mechanism of narcosis,[8] it was observed that unlike nitrogen and argon at increased pressures, helium did not adsorp to the monolayer, even at depths in excess of 3,000 ft.

It was suggested therefore, in agreement with Carpenter, that helium is unlikely to produce signs and symptms of narcosis similar to most other inert gases.

Nevertheless, early in 1965, during experiments with men compressed with oxygen-helium at 100 ft/min to 600 ft for 4 hrs,[2] decreases were noted of 18% in arithmetic and 25% in a test of fine manual dexterity, which were twice as severe at 800 ft. This performance decrement was accompanied by dizziness, nausea, vomiting and a marked tremor of the hands, arms and even whole body which came to be called "helium tremors," but is probably more correctly called just "tremors" as the cause appears to be due to pressure per se.[18] Unlike

compressed air intoxication, in 1½ hrs the condition of the subject had returned to normal. Later at depths between 300 ft and 500 ft[9,10] the presence of tremors associated with helium deep diving were confirmed. Much speculation arose as to the cause but the condition was noted to be markedly reduced if the rate of compression was slow. Thus, with a compression time of 24 hrs, a simulated depth of 1,000 ft was attained for the first time at Duke University[23,24] without the appearance of tremors or related symptoms.

In the same year however, a simulated dive to 1,189 ft was aborted after only 4½ mins at depth, due to the appearance of unusual signs and symptoms in the two men concerned.[11] Involving a two-hour compression, the dive was abandoned due to the onset, at depths greater than 1,000 ft, of a marked increase in slow theta activity (4-8 c/s) in the electroencephalogram (EEG), tremors and microsleep characterised by brief periods of somnolence if the subject was inactive. Earlier studies with monkeys[12] had resulted during deep oxygen helium dives in first the appearance of tremors, followed by periods of somnolence and finally convulsions. These signs and symptoms were labelled the High Pressure Nervous Syndrome (HPNS) and a "Helium Barrier" to human diving was considered to probably exist at 1,200 ft.

Conversely, with slow compression, mice and rats have been exposed successfully to over 4,000 ft without convulsing[21] and other work has established that the associated hyperthermia of rapid compression enhances the risk of tremors and convulsions.[27] Further, in February 1969 three Swiss divers spent three days at 1,000 ft with a total of 5 hrs of excursions underwater to 1,150 ft.[13] Except for some initial tremors at 1,000 ft no serious limitations of performance were noted and the men were able to swim and work underwater with unexpected ease.

The present dive to 1,500 ft therefore was planned with three interim stages, two of 24 hours at 600 ft and 1000 ft and one of 22 hours at 1300 ft to enable thorough physiological, psychological and medical studies with special emphasis being given to the EEG and tremor phenomena. Temperature increases were to be not more than 5°C. It was hoped thus to determine the aetiology of the HPNS when diving both very deep and also at Continental Shelf depths and to ascertain if man could safely dive deeper than 1,200 ft.

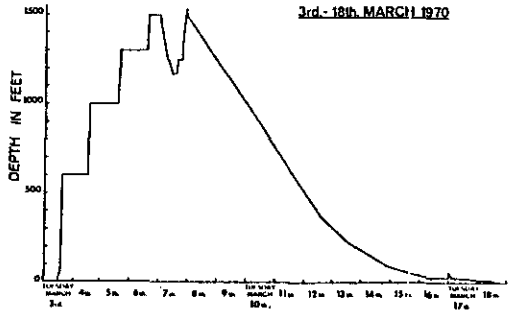


Fig. 1. The profile for the simulated dive of 10 hours at 1,500 ft involving 24-hr stages at 600 ft, 1,000 ft and 1,300 ft and 1-hr stages at 1,100 ft, 1,200 ft and 1,400 ft with 10 hrs at 1,500 ft. The recompression during decompression due to a vestibular bend in Sharphouse is shown during the first two days of decompression.

Preliminary investigations were carried out also at 100 ft, 300 ft and 450 ft, each for 24 hrs at that depth. Details of the neurophysiological,[6] biochemical,[5] respiratory,[22] and other data[7] are given elsewhere. This paper will be restricted to the studies of performance efficiency during these dives.

METHOD

The pressure chamber for the experiments consisted of two compartments, the larger living compartment having a volume of 225 cu. ft. The total chamber length was 16 ft with a 5 ft 6 ins diameter. The chamber atmosphere was maintained within the following levels:

Oxygen—0.45 ats abs
Carbon dioxide—less than 0.5% equiv. 1 ats.
Nitrogen— less than 2.0% equiv. 1 ats.
Helium—remainder
Relative humidity—70—90%

No heating was available during the preliminary dives to 100 ft, 300 ft and 450 ft when the chamber temperature was about 25°C. Extra clothing was worn in an attempt to maintain thermal equilibrium. During the 1,500 ft experiment the pressure chamber was heated by electrical cables which were wound around the outside of the vessel, and insulated by covering with fibreglass. This enabled the temperature to be maintained at 30°C during the stable phases of the dive and not to exceed 35°C during compression.

Except for the 100-ft dive, the same two subjects from the RNPL staff were used throughout. The younger, Peter Sharphouse (PS) was aged 21 and relatively inexperienced as was his replacement, Peter Macaulay (PM), during the 100 ft dive. The other subject, John Bevan (JB) was aged 27 and had considerable recreational diving experience, although not in the saturation mode.

The four dive profiles naturally varied but the compression rate was 16—17 ft/min throughout. The preliminary dives involved 24 hours at 100 ft, 300 ft and 450 ft. For the 1,500 ft experiment stages of 24 hours were spent at 600 ft and 1,000 ft and 22 hours at 1,300 ft with 1 hour stages at 1,100 ft, 1,200 ft and 1,400 ft, culminating in 10 hours at 1,500 ft (Fig. 1).

A battery of tests were evolved for measuring performance and finger tremors so as to permit careful monitoring of any changes which might indicate the occurrence of the HPNS or other problems which might necessitate stopping the dive in the interests of the safety of the subjects.

Performance Tests

Ball Bearing Test—The subject was required to pick up ball bearings with tweezers and place them, one at a time, in a tube. Time for the test was one minute and the score the number of balls in the tube. Previous work has established the value of this test in quantifying the effects of tremors.[9,10,13]

Tremor Transducer. A Specialised Laboratory Equipment TREM 1 Tremor Transducer was attached by a rubber sheath to the middle finger of the subject, who held his forearm and hand stretched out straight in front, while his elbow rested on his leg. The output of the transducer, which measured the velocity of the postural tremor, was fed to an E8A Galileo Electroencephalograph and recorded on paper. The output also was recorded on a Philips Analog 7 FM instrumentation tape recorder and analysed subsequently into five activity bands, namely Delta (2-4 c/s), Theta (4-8 c/s), Alpha (8-13 c/s), Beta 1 (13-20 c/s) and Beta 2 (20-30 c/s), by means of a Nihon Kohden EEG Frequency Analyser.

Purdue Peg Board Test—In one minute as many pegs and washers as possible had to be assembled in holes on a board. The score was the number of parts assembled; each complete item consisting of one peg, two flat washers and a spacer, all threaded over the peg. Each item thus had a score of 4.

Towse Touch Test—While blindfolded, in one minute the subject sorted two sizes of ball bearings which also had different textures. The score was the sum of correct balls sorted in the right and left trays minus the errors.

Wechsler Bellevue Digit Symbol Test (Visual Analogies)—The subject was required to relate symbols to a set of numbers from 1 to 9 given in a key. The score in one minute was the number of correct answers.

Arithmetic Test—In two minutes the subject answered as many sums as possible of two figure by one figure multiplication. The sheets of sums were provided by computer using random numbers. The score was the number of sums correct and the number attempted.

Personal Comment Check List—The deep diving questionnaire developed by Weybrew and Parker[26] was completed by each subject at regular intervals, together with their assessment of the effects of the environment and pressure upon themselves.

RESULTS

It should be remembered that the 100-ft, 300-ft and 450-ft dives were primarily to permit the scientific teams and subjects to become familiar with the techniques to be used and to assist co-ordination of the many teams concerned in the record 1,500 ft dive. Thus, not all the test battery was used in some of the preliminary dives.

The compression in stages in the final dive to 1,500 ft proved most successful and permitted the planned depth to be reached for the first time. As reported elsewhere[11] theta activity was increased in the EEG, especially during each compression phase. Indeed, once initiated, theta continued to increase in quantity for some six hours before slowly reducing to lower values over a further 12 hours. Thus the introduction of the three stages, primarily to facilitate the many detailed scientific measurements, in fact materially assisted the successful achievement of reaching 1,500 ft by allowing sufficient time for adaptation and permitting the EEG changes to resolve rather than continue to increase to dangerous levels, as probably would have occurred if compression had been continuous to 1,500 ft.

During the decompression, which began at 40 ft/hr under the supervision of Surg. Cdr. Barnard, vestibular decompression sickness occurred in PS characterised by vertigo, nausea, vomiting and photophobia. On recompression, eventually to 1,535 ft, in an unsuccessful attempt to resolve this problem, subject JB reported a sensation of impending loss of consciousness in which only by earnest concentration and keeping busy could he maintain consciousness; a condition similar to the 'microsleep' reported in the earlier dive to 1,189 ft.[11]

On immediate decompression from 1,535 ft at 10 ft/hr, this sensation disappeared and was accompanied by a gradual improvement in subject PS. At 625 ft JB complained of an ache in his right leg, thought at first to be due to lack of exercise, but which became more acute on the 10th day (Figure 1). Thereapeutic recompression resulted in no improvement and the decompression profile was continued, both subjects reaching the surface in satisfactory condition.

The results of the performance tests for each depth will now be considered separately.

Exposure to 100 ft Oxygen-Helium for 24 hours—The performance tests showed evidence of learning in both PM and PS as neither subject had sufficient pre-dive practice to achieve a stable base-line (Table I). However of the two subjects, PS was the more practised. His

TABLE I. PERCENTAGE CHANGE IN PERFORMANCE TESTS DURING 24 HR/100 FT/OXYGEN-HELIUM DIVE (O_2 0.45 ats abs)

TEST	SUBJECTS	1 hr at 100 ft	2 hrs at 100 ft	4 hrs at 100 ft	10 hrs at 100 ft	22 hrs at 100 ft	DECOMPRESSION 70 ft	DECOMPRESSION 10 ft	SURFACE RETURN	SURFACE RETURN
BALL BEARING	P.M.	+ 11.1	0	+ 11.1	0	+ 5.6	+ 16.7	+ 44.4	+ 38.9	+ 50
	P.S.	− 14.3	− 14.3	+ 14.3	+ 35.7	+ 42.9	+ 64.3	+ 85.7	+ 71.4	+100
TOUCH TEST	P.M.	+ 44.5	+ 9.1	+ 40.9	+ 77.3	+ 54.5	+ 81.8	+ 77.3	+ 4.5	+ 31.0
	P.S.	− 25.5	− 15.7	− 7.8	0	− 13.7	− 13.7	− 5.9	− 11.8	0
PEG BOARD	P.M.	+ 5.8	+ 1.9	+ 7.7	0	+ 7.7	+ 7.7	− 5.8	+ 7.7	− 11.5
	P.S.	+ 7.0	+ 1.8	+ 10.5	+ 3.5	+ 10.5	+ 5.3	+ 5.3	+ 12.3	+ 19.3
VISUAL ANALOGY	P.M.	− 7.3	− 16.4	− 10.9	− 9.1	− 12.7	− 12.7	− 9.1	− 10.9	− 7.3
	P.S.	− 18.5	− 16.7	− 14.8	− 7.4	− 7.4	− 7.4	− 7.4	− 9.3	0
ARITHMETIC CORRECT	P.M.	− 9.5	− 14.3	− 9.5	− 19.0	− 19.0	− 4.8	− 4.8	+ 4.8	− 9.5
	P.S.	+ 83.3	+150.0	+100.0	+150.0	+183.3	+200.0	+233.3	+200.0	+216.7
ARITHMETIC ATTEMPTED	P.M.	− 9.5	− 14.3	− 9.5	− 14.3	0	+ 9.5	+ 9.5	+ 4.8	− 4.8
	P.S.	+ 66.7	+ 77.8	+ 55.6	+ 77.8	+100	+100	+144.4	+111.1	+122.2

results at 100 ft showed some impairment in the sensitive manual tasks such as the Ball Bearing Test and Touch Test, with recovery after about four hours. The less sensitive Peg Board Test was unaffected as was the Arithmetic Test, which showed strong learning characteristics. Performance at the Visual Analogy Test in both subjects showed a general deterioration compared with controls both throughout the time at pressure and the decompression. However the heavy learning and erratic performance at the tests during this first preliminary dive do not permit definite conclusions other than some loss of manual dexterity in PS during the first hours at 100 ft.

Personal Comments and Deep Diving Questionnaire —The checklists during this experiment were only completed at the 10 ft stop and on return to the surface. At

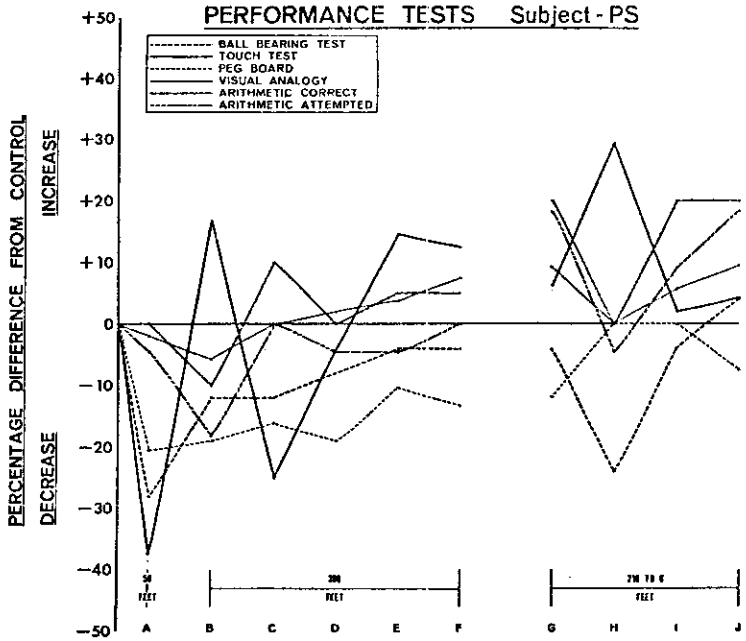


Fig. 2. Performance efficiency in subject PS during exposure to 300 ft oxygen (0.45 ats abs) and helium for 24 hours and during the decompression. Test period A, given at 50 ft, B, initial hour at 300 ft, C, 3rd hour, D, 6th hour, E, 10th hour, F, 21st hour. During decompression G at 210 ft, H at 65 ft, I at 36 ft. Test J was given on the surface in the laboratory.

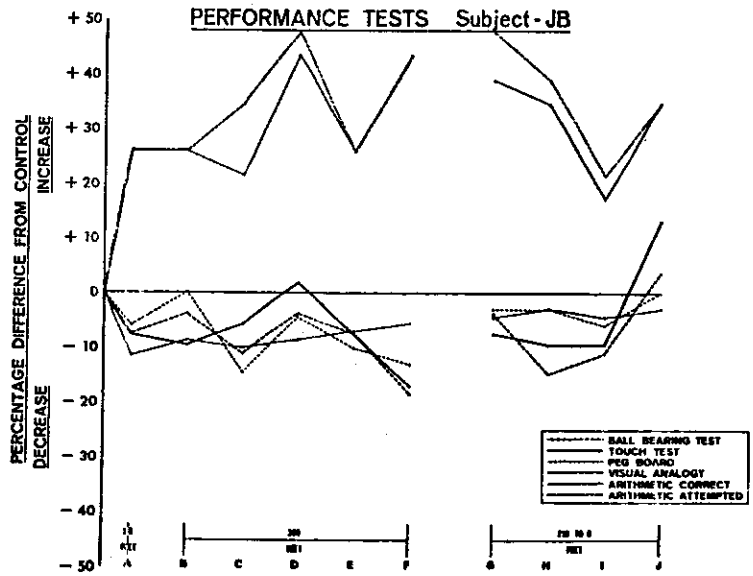


Fig. 3. Performance efficiency in subject JB during exposure to 300 ft oxygen (0.45 ats abs) and helium. Test periods A-J as for Figure 1.

10 ft PM felt "good, satisfied, tired, light-headed but no difficulties". He had managed 8½ hours sleep in the previous 24 hours. On reaching surface he again indicated no difficulty and felt good but irritable, with dizziness and a lighthead sensation. Four and a half hours later his questionnaire indicated good, satisfied irritable, light-headed, ringing in the ears, no difficulty.

At the 10-ft stop PS felt good with no difficulty and had 6-7 hours sleep during the previous 24 hours. On the surface he felt good and satisfied but indicated he had a headache and blurred vision. Four and a half hours later his comments were the same.

Exposure to 300 ft Oxygen-Helium for 24 hours, Performance Efficiency—The tremor transducer indicated no significant increase, inferring that finger tremors were not present in either subject. No serious impairment in efficiency at the various performance tests was observed as a result of exposure to 300 ft 0_2/He. Subject PS showed strong learning characteristics and a fall in all tests performed which was most evident in those of manual performance, such as the Ball Bearing Test, Touch Test and Peg Board, when carrying out the tests at 50 ft inside the pressure chamber, rather than in the laboratory (Figure 2).

JB showed a similar decrement as a result of carrying out the tests in the chamber at 50 ft which was less than PS and was not made worse by exposure to 300 ft (Figure 3). The Arithmetic test showed a marked improvement in the results of the tests in the pressure chamber compared with the laboratory.

Exposure to 450 ft Oxygen-Helium for 24 hours, Performance Efficiency—The subjects showed much less evidence of any learning pattern during this experiment compared with the 300 ft dive. In general PS (Figure 4) was more erratic in his tests of performance than JB (Figure 5), as was the case in fact throughout the dive series.

Subject JB exhibited a decrement during exposure to 450 ft which primarily affected the tests of manual dexterity. The greater sensitivity of the test the more was it affected. Thus the Ball Bearing and Touch tests were reduced the most, with a slow recovery during decompression. This was followed by a smaller decrement with the Peg Board Test and little or no effect on the Visual Analogy Test. The Arithmetic Test showed an increase of some 10% due, in part, probably to the relatively 'isolated' conditions of the 50 ft test in the pressure chamber allowing greater concentration than the controls conducted in the laboratory. On comparison against the 50-ft controls it was only the tests of manual dexterity which were slightly affected due to mild hand tremors.

The tremor transducer, although not entirely satisfactory due to technical difficulties, did indicate a small in-

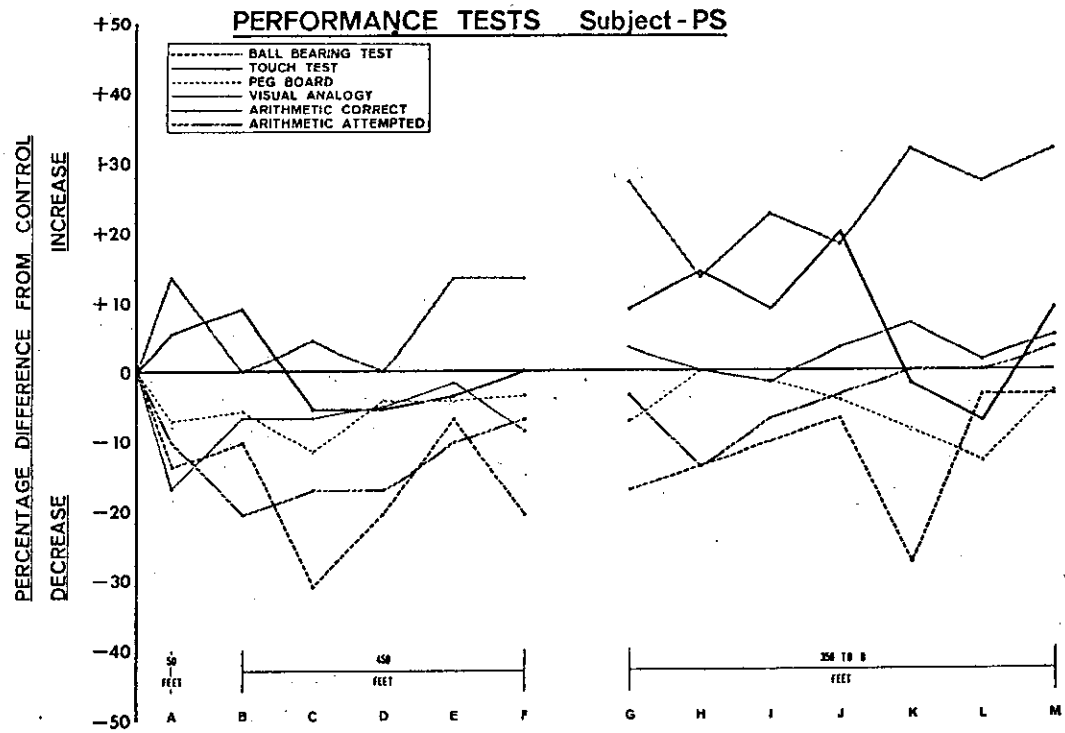


Fig. 4. Performance efficiency in subject PS during exposure to 450 ft oxygen (0.45 ats abs) and helium. Test periods A-F as for Figures 1 and 2. During decompression G at 350 ft, H at 190 ft, I at 137 ft, J at 52 ft, K at 34 ft, L at 1.5 ft and M on the surface in the laboratory.

crease in the amount of tremors which varied between 50–100% greater than pre-dive values in both subjects.

On the basis of comparison with the controls at 50 ft, where conditions are the same rather than to the laboratory controls, the most seriously affected test was the Ball Bearing Test. This, as already discussed, is no doubt due to the mild tremors. With the exception of the number of arithmetic sums attempted, the other tests showed little significant change. During decompression the test results improved to normal or greater than normal values.

Exposure to 1500 ft Oxygen/Helium, Finger Tremors—The amount of tremors measured by the finger tremor transducer was quite different for each subject (Figure 6). JB showed marked postural tremors whereas PS was affected only to a minor extent. The tremors were considerably enhanced by each of the compression phases and during the early morning on waking. The changes were in amplitude rather than frequency, all the activity bands showing similar increases. In Figure 6 is shown the mean change of the five activity bands.

At 600 ft JB had a 100% increase in tremors over controls. This, initially at 1,000 ft, increased to 400% but within 2 hours was reduced to 75% of normal. Compression through 1 hour at 1,100 ft and 1,200 ft to 1,300 ft resulted in a further increase in tremors to 600% of controls. Again this returned in a few hours to a lower value of 125%. After 1 hr at 1,400 ft compression to 1,500 ft resulted in a less marked increase in tremors of some 275% with a reduction to a value somewhat greater than the stable value at 1,300 ft.

Thus, in general, JB showed large increases in postural tremors on compression, which soon settled to lower values, but these more stable levels of tremor tended to become worse with increasing depth and were accompanied by an intention tremor. With PS, tremors were never more than 100% greater than controls and the effect of compression was less obvious.

Performance Efficiency Tests—The results of the tests of performance efficiency show that during the nine months of preliminary experiments the subjects had practiced sufficiently to overcome learning effects and most of the decrement in performance was in tests of fine manual dexterity such as in the Ball Bearing Test, the Peg Board Test and the Touch Test. The worst impairment was immediately after compression. Mental tests, such as the Arithmetic and the Visual Analogies Tests virtually were unaffected.

Thus, in the Ball Bearing Test, PS, on compression, showed a peak decrement at 1000 ft of 50% which soon recovered to 20–25% less than normal (Figure 7). Thereafter, with minor peak depressions of efficiency on compression, a decrement averaging 30% was maintained. During decompression from 1,100 ft to 800 ft, as a result of vestibular decompression sickness, there was a greater decrement of 45%, which returned to control

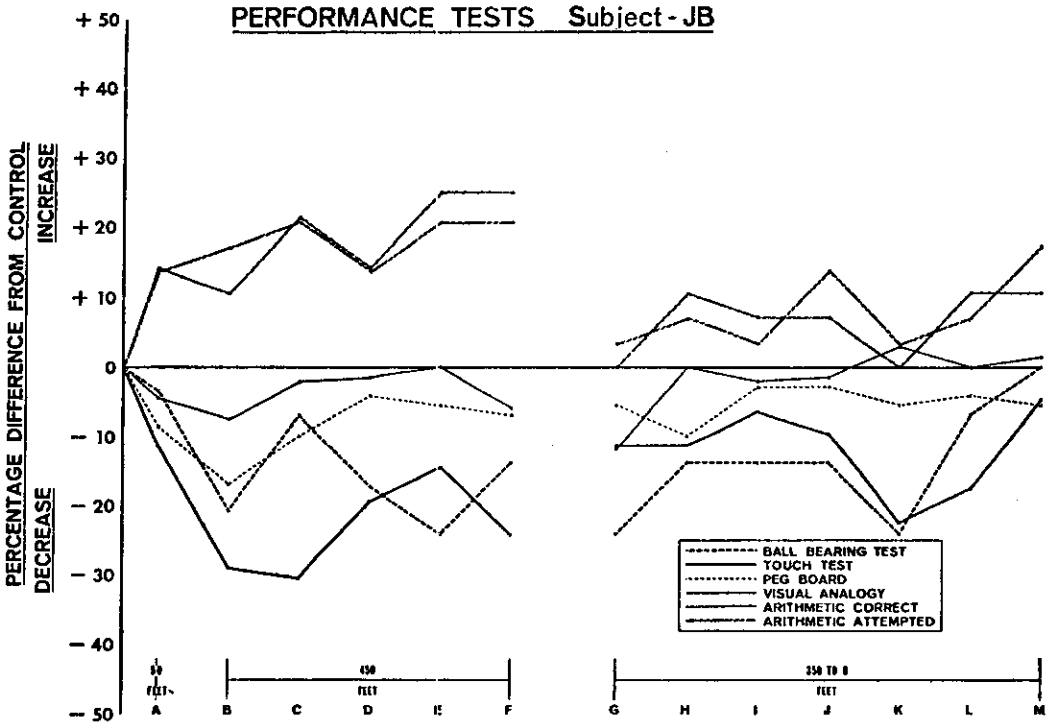


Fig. 5. Performance efficiency in subject JB during exposure to 450 ft oxygen (0.45 ats abs) and helium. Test periods as for Fig. 4.

values on return to the surface. The Touch, Peg Board and Visual Analogy tests were depressed by only some 10–15% below surface performance and except for an additional fall to 20% during the initial decompression, performance returned to control values on reaching the surface. No significant changes were observed in the Arithmetic Test, except during the initial decompression, when, due to the vestibular decompression sickness, a 20% reduction occurred in both the number of sums correct and attempted.

The performance of JB was more seriously impaired (Figure 8). However, again the Arithmetic Test was unaffected and the Visual Analogies test was rarely depressed by more than 10% but the tests of manual dexterity were markedly depressed.

With the Ball Bearing Test, on compression to 1,000 ft, the initial decrement of 45% soon recovered to only 20% but compression again to 1,300 ft resulted in a 55%

Fig. 7. Performance efficiency in subject PS during stage compression and exposure to 1,500 ft oxygen (0.45 ats abs) and helium and subsequent decompression. Test period A given at 50 ft, B initial hour at 600 ft, C, 2 hours, D, 4 hours, E, 9.5 hours, F, 19.5 hours. Test G initial hour at 1,000 ft, H at 6 hours, J, 10 hours and K, 21 hours. Test L during the hour at 1,100 ft and test M the hour at 1,200 ft. Test N initial hour at 1,300 ft, 0 at 2 hours, P, 3 hours, Q, 8 hours and R, 18 hours. Test S during hour at 1,400 ft. Test T during first hour at 1,500 ft, U at 2 hours. V at 5 hours and W 7 hours. Tests A to K during decompression from 1,100 ft to surface. A, 1,100 ft, B, 1.050 ft, C, 858 ft, D, 623 ft, E, 565 ft, F, 388 ft, G, 228 ft, H, 31 ft, I, 24 ft, J, surface, K, surface.

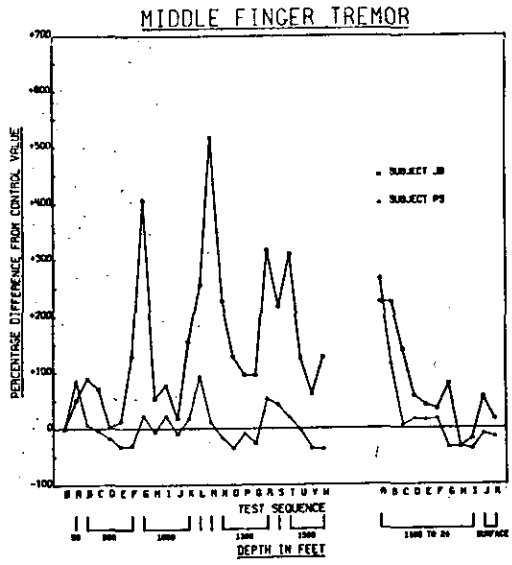
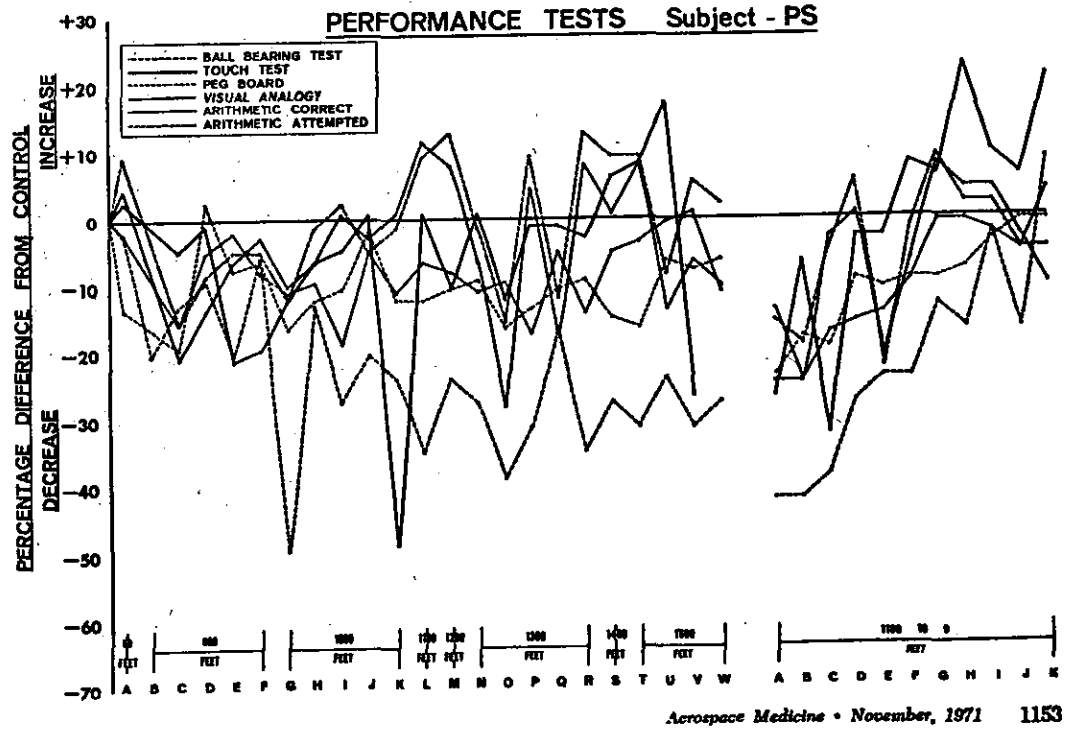


Fig. 8. Percentage change in the mean of the activity bands Delta, Theta, Alpha, Beta 1 and Beta 2 indicating the change in velocity of finger tremor during stage compression to 1500 ft with oxygen-helium. Subject PS is unaffected but JB shows an increase in base-line tremor plus peaks associated with compression.



decrement which recovered to 25% less efficient than controls. On compression to 1,500 ft the peak decrement was almost 70% recovering to a value 35% of normal.

Performance at the Touch Test gave a 25% decrement and Peg Board efficiency was reduced by 15–20%. However, efficiency as a whole at these tests was no worse at 1500 ft than between 600 ft to 1,000 ft.

In general the decrement in performance mainly involved manual dexterity and appeared to be due to the tremors. Tests of mental efficiency virtually were unaffected.

Personal Comments—Analysis of the personal comment check list showed a high level of morale throughout the dive with, in both men, frequent comments of "good" or "happy". No behavioural or psychological problems occurred during the 15 days.

Subject JB at 600 ft mentioned inefficiency due to tremors, clamminess of the hands and feeling too warm on compression (35°C). "Clicks" were noted in the right knee joint during exercise on a bicycle-ergometer. Some 5½ hours of good sleep were obtained and there was no respiratory difficulty. During the first two hours at 1,000 ft. tremors were reported again with light-headed sensations, dizziness and slight nausea. Clamminess was mentioned again and 6½–7 hours of good, though interrupted sleep recorded. At 1,200 ft. periodic muscle jerks of the limbs occurred and jerky voluntary movement were noted. Appetite remained excellent and taste of food normal. At 1,300 ft Bevan reported waking frequently during the night and having vivid dreams. As previously he noted involuntary muscle jerks, feeling warm and an inability to achieve adequate ventilation when breathing through the nose. Orientation was reported as excellent.

PS also reported dizziness, nausea and clamminess during the first two hours at 600 ft. Sleep was poor, with only four hours during the first night. On compression to 1,000 ft. the dizziness returned for the first hour. Sleep improved to a fair six hours. Temperature regulation was difficult, as only slight variations around the chamber temperature of 29–30°C caused comments of feeling either too cold or too warm. At 1,300 ft. PS also reported feeling a need to breathe through the mouth, and a small amount of movement was noted to quickly induce fatigue.

DISCUSSION

The results support the view based on the work of Carpenter[14] and in vivo studies of the penetration of lipid monolayers by inert gases[8] that helium does not induce signs and symptoms of narcosis similar to those produced by increased pressures of nitrogen or argon. At 1,500 ft the tests of mental performance showed no significant decrement indicating no helium narcosis. However signs and symptoms of the HPNS did occur, including "tremors" which were responsible for a decrement in manual dexterity and motor coordination. In

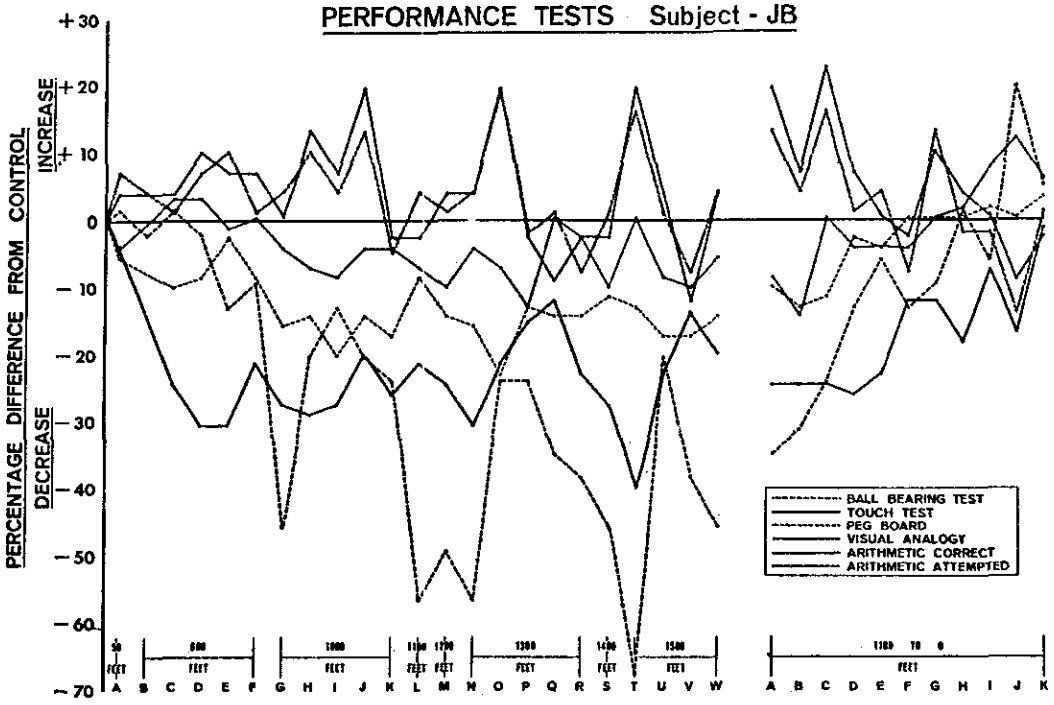


Fig. 8. Performance efficiency in subject JB during stage compression and exposure to 1,500 ft oxygen (0.45 ats abs) and helium and subsequent decompression. Detail as for Fig. 7.

general the decrement was not much more severe at 1,500 ft (Figs 7 and 8) than at 450 ft (Figures 4 and 5), although in JB each compression phase resulted in peaks of marked deterioration in manual dexterity (Figure 8), which correlated with the peaks of marked increase in tremor as indicated by the tremor transducer (Figure 6). That JB, in addition, showed an overall increase in base-line tremor 100% in excess of controls also would seem to account for his greater decrement in dexterity compared to PS who virtually was unaffected by tremors during the 1,500-ft experiment.

Now slow compressions of say 24 hours to 1,000 ft, as used in the experiment at Duke University,[23,24] should stop the appearance of tremors and result in no deterioration in performance. Whether, however, other signs of the HPNS, such as the increase in theta activity of the EEG would similarly be prevented remains to be seen. After 18 hours the theta level was returning toward normal but other neuro-physiological measurements, such as the averaged cortical auditory evoked response showed a steady decline in the functional integrity of the brain.[6]

The incidence of tremors also could be decreased in future deep dives by carful selection of subjects. In the present dive PS clearly was able to tolerate the compression more than JB and showed hardly any tremors.

The lack of mental decrement again appears to be a function of the rate of compression. The provision of the 24 hour stages were no doubt also of assistance. Zaltsman[27] has reported that compressions of 30–60 ft/min to depths of 220-630 ft oxygen-helium, with oxygen partial pressures between 1.4–2.0 ats abs. resulted in impairment of mental efficiency, memory, motor reflex and dimensions of writing similar to those reported earlier by Bennett[2,3] with a compression rate of 100 ft/min. These decrements occurred without the appearance of EEG changes. The present compression rate of 16-17 ft/min seems adequate to eliminate the mental deterioration but not the motor, and this would agree with the findings from other experiments involving compressions of one hour to 1000 ft,[13], 40 mins to 700 ft[25] and 60 mins to 650 ft.[17]

In connection with the tremors and psycho-motor decrement, Zaltsman report in a study with mice[27] that fine tremors appeared at 30–40 ats which soon disappeared. On compression they reappeared again, as in man, but once more soon disappeared. However, at 75–105 ats the tremors developed into persistent convulsive movements of the whole body, rather than the separate clonic spasms of the extremities seen at 40–75 ats, and the former gradually increased in frequency and duration. At 65–120 ats the animals tended to collapse with legs splayed, showed impaired coordination of movement and responded to taps on the pressure chamber with generalised clonic spasms resembling epilepsy. Similarly, Lever, Miller, Paton and Smith[19] noted that mice at a compression rate of 300 ft/min showed tremors at 35–50 ats, convulsions at 70–80 ats and death at about 136 ats whereas a rate of 15–16 ft/min resulted in tremors at 75–109 ats, convulsions at 105–120 ats and death at 159 ats.

It is evident therefore on the basis of the present study and the earlier work that it is possible with slow compression to dive very deep with the minimum of tremors, no mental deterioration and no convulsions. Conversely fast compression results in early appearance of tremors, hyperexcitability, mental confusion, somnolence and eventually convulsions. How deep man can dive with safety by slowing the compression and introducing stages to permit adaptation remains to be determined but it would seem likely that convulsions may be the critical factor limiting deep oxygen-helium diving.

It is relevant that confusion and tendency to somnolence occurred in JB at 1535 ft during the recompression to try to ameliorate the signs and symptoms of the vestibular decompression sickness in PS. The pressure was increased in a series of short compressions and stages over about 8½ hours from 1160 ft to 1535 ft (Figure 1). Similar signs and symptoms were termed "microsleep" by Brauer[11] during compression from 1,000 ft to 1,189 ft in just over 37 minutes.

If this rate of compression had been applied to JB his compression time would have been 1 hour 15 minutes but, although to a greater depth, he actually took 8½ hours. When compared to the original rate of compression to 1,500 ft this is still fast, as compression from the 1,200 ft to 1,500 ft levels, inclusive of the 24 hour stage at 1,300 ft, took some 26 hours 18 minutes.

When it is considered that 20 hours at stable pressure are required for the EEG changes to resolve, failure to permit such adaptation may well result in severe disruption of the function of the brain, leading to narcosis, "microsleep" or possible even convulsions. Thus it would seem advisable to incorporate 24-hr stages in the compression phase of very deep oxygen-helium dives as well as a relatively slow rate of compression. Alternatively a very slow rate of compression indeed may be sufficient to permit enough adaptation for most practical purposes.

A further alternative based on work by Brauer[11,12] and Zaltsman[27] is to add small amounts of a narcotic inert gas such as nitrogen or argon. Thus a mixture of 8.2% oxygen, 27% nitrogen and 64.8% helium at 17.5 ats resulted in no tremors but only EEG and performance changes commensurate with the 5 ats nitrogen. Every effort should also be made to restrict the temperature increases as a rise in temperature appears to accelerate the signs and symptoms of HPNS.

These experiments have confirmed that helium is not a narcotic like nitrogen and consideration as to the cause of the HPNS and related psychomotor effects must therefore be due to another factor. The most likely cause would seem to be the pressure itself. This is difficult to prove in mammals. However recent work on newts and mice[19] together with earlier experiments by Kylstra, Nantz, Crowe, Wagner and Saltzman[18] and MacInnis, Dickson and Lambertsen,[21] involving such experiments as hydraulically compressed fluorocarbon-breathing mice, appear to confirm the role of high pressure per se as the cause of the HPNS and not any pharmacological action of helium.

ACKNOWLEDGEMENTS

Grateful appreciation is extended to Mr. J. Bevan and Mr. P. Sharphouse, the subjects of the pioneering exposure to 1500 ft, to Mr. A. N. Dossett and Miss B. Andrews for their technical assistance, to the pressure chamber control teams under the direction of Mr. J. Eaton and the Medical Safety Officers under the direction of Surg. Cdr. E. E. P. Barnard, RN, without whom it would not have been possible to carry out the long and complex saturation diving experiment described in this paper.

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Reprinted from *The Military Surgeon,* Vol. 103, No. 2, August, 1948

THE PREVENTION OF DECOMPRESSION SICKNESS AND NITROGEN NARCOSIS BY THE USE OF HYDROGEN AS A SUBSTITUTE FOR NITROGEN (THE ARNE ZETTERSTRÖM METHOD FOR DEEP-SEA DIVING)

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(With one chart)

Background

HELIUM has become widely used as a substitute for the nitrogen in the breathing air in the treatment of pulmonary diseases as well as for the prevention of decompression sickness. It is now well established that helium has a definite advantage in many clinical and physiological applications owing to its decreased breathing resistance, its shorter elimination-time for the tissues, thus allowing more rapid decompression, and its slight narcotic effect at high pressures compared to that of nitrogen. While the favourable actions from low inhalation resistance and rapid elimination from the body tissues have exclusively interested the clinician and the aviation physiologist respectively, all the above advantages of helium come into play when the gas is employed in deep-diving.

It seems now that, after the introduction of helium as a substitute for nitrogen in deep-diving operations, the safe depth limits in the open sea are set less by physiological factors than by technical difficulties. Since such difficulties will often come into play even at depths which do not exert serious physiological stress on experienced divers using air and ordinary diving dresses, the administration of helium may be considered more or less an emergency method reducing only the physiological hazard beyond depths where airbreathing is not too risky.

It is, however, obvious that, for instance, the rescue of the crew in a submarine which can not be maneuvered to the surface, will necessitate all possible efforts, at least in peace time. Rescue bell equipment available during the salvaging operations may not eliminate the assistance of deep-divers for the localization of the submarine, and for the fastening of the bell. Therefore, the Royal Swedish Navy, who has constructed and developed bells similar to those of the U. S. Navy, has been especially interested in the problem of reducing the hazards in deep-diving operations. Owing to the unfortunate circumstances that, during the war, helium could not be imported from the U.S. in sufficient quantities for deep-diving purposes, the physiological and technical possibilities of substituting hydrogen instead of helium for nitrogen were investigated. A method was adopted in 1943 as the result of a suggestion by the late A. Zetterström.

Although certain properties of hydrogen have led to the mention of this gas in the literature in connection with theoretical considerations in the field of deep-diving physiology, the great risk for explosion in the handling of hydrogen-oxygen mixtures seems to have discouraged the testing of this gas for deep-diving purposes. This risk can, however, be avoided if, as already pointed out by *Case & Haldane, 1941,* the oxygen percentage is kept at 4 or below. In the method independently proposed by *Zetterström,* the procedure should involve the use of hydrogen only below depths where the oxygen pressure is high enough to allow sufficient supply to the diver, but where the oxygen percentages are kept below the limit for risk of explosion.

Theoretical Considerations

In the preliminary theoretical treatment of the problem of hydrogen-diving, assump-

tions had to be made for the calculation of decompression tables in certain connections where definite reliable information concerning the physical and physiological properties of hydrogen was not available. Since then further data have been collected, especially from the researches on decompression sickness made during the war within the field of aviation medicine, and which have now been released. However, for completion of the following theoretical introductory sections, reference will be made also to such papers which were not available at the time when the hydrogen method was developed.

1. *General suitability of hydrogen as a diluent of inhaled oxygen*

Hydrogen may be inhaled together with the necessary supply of oxygen without causing any harm at ordinary atmospheric pressure. No ill-effects from inhalation of hydrogen have been reported, and the gas may therefore physiologically be compared with nitrogen. Although both gases readily combine with many substances, they seem to be as chemically inert in the body after inhalation as the noble gases, of which there are no known compounds. Hence, it may be assumed that hydrogen, when inhaled together with oxygen, acts merely as a diluting agent similar to the nitrogen of ordinary air, both vehicles being absorbed and eliminated by the body through physical rather than chemical properties. In the case of hydrogen the foundation for this assumption may, however, be less certain than for nitrogen, which has been shown to be almost completely recovered from the body when oxygen is breathed (*Behnke, Thomson & Shaw, 1935*).

Since hydrogen is odourless, inhalation of the gas can only be perceived and recognized by certain other physical properties. As described by *Case & Haldane* (1941), the gas may feel unpleasantly cold to breathe due to its high heat conductivity. Owing to the low molecular weight of the gas, a considerably decreased inhalational resistance is noticed at high pressures when compared to that of nitrogen. The increased velocity of sound in hydrogen also raises the pitch of the voice, which becomes nasal and indistinct. These properties will be considered below in the discussion of the practical utilization of the gas for deep-diving.

2. *Gas uptake and elimination*

Mechanism of dissolved gas exchange in general. The body tissues at sea level contain approximately 0.01 volumes "S.T.P." of dissolved nitrogen per volume of non-fatty tissues and approximately 0.05 volumes per volume of fatty tissue (*Bornstein* 1913, *Campbell* and *Hill* 1931, *Grollman* 1932, *Behnke* 1942). Changes in barometric pressure are followed by re-equilibration of the dissolved nitrogen to extents proportional to the nitrogen partial pressure of the gas inhaled, compressed air causing a movement of nitrogen from the lungs into the tissues and decompression an outward transfer. Effective elimination of dissolved tissue nitrogen can thus be brought about by inhalation of pure oxygen because of the subsequent nitrogen transfer via the venous blood to the pulmonary alveoli, where the nitrogen partial pressure is zero and nitrogen therefore is washed out by the pulmonary ventilation.

For a long time attempts have been made to analyze experimentally and describe mathematically the course of gas uptake or elimination by the body as a whole when the ambient nitrogen partial pressure is raised or lowered. *Zuntz* (1897), *Heller, Mager,* and *v. Schrötter* (1900), and *Boycott, Damant, & Haldane* (1908) were the first to recognize the logarithmic decay in the rate of gas exchange as related to time. However, it is now well established that the logarithmic relationship is only approximative. The body-gas exchange curve obtained for inert gases can not be represented by a single exponential expression but is the sum of several exponential components. With a certain simplification, gaseous nitrogen elimination from the body as a whole during

the course of oxygen inhalation may be considered to follow a curve which is the sum of two hypothetical exponential curves (*Behnke*, 1945), representing the elimination of nitrogen from the body solvents, "fluid" and "fat." Since the decay of the "fluid" curve is more rapid, the later part of the "whole-body" curve is substantially the "fat" component, whereas the beginning of the nitrogen elimination curve is the resultant of "fluid" and "fat" components. If the body-gas exchange curve is expressed as

$$R_t = R_o e^{-kt} \qquad (1)$$

where R_t = rate of elimination after time t (cc of gas per minute), R_o = rate at the beginning of elimination, k = constant of elimination (time-constant), e = base of natural logarithm, and experimental values for nitrogen elimination are substituted, the value of k is found not to remain constant but to decrease progressively, the shape of the curve thus differing from those of its hypothetical and exponential components, having its own constant k.

In the above example reference was made only to two types of body solvents, one yielding a higher k than the other, and consequently a higher rate of gas exchange. The component curves are only approximations of the manner in which nitrogen is absorbed by, or eliminated from, its chief body solvents. That, in the course of nitrogen exchange, different kinds of tissues have different rates of exchange, was arbitrarily assumed by *Boycott, Damant & Haldane* (1908). In computing decompression tables for divers, they assumed the existence of tissues which half saturate or desaturate with nitrogen in 5, 10, 20, 40, and 75 minutes, while admitting the possibility of even slower tissues. That saturation and desaturation curves should be reciprocal was indicated by *Boycott et al.* and shown experimentally by *Shaw et al.* (1935). The latter further showed that N_2 absorption obeys Henry's law. The arbitrary "tissues" were believed to differ with respect to solubility for nitrogen and blood perfusion, each kind of tissue being characterized by its own exponential exchange rate. Thus the slowest tissues would have a great solubility for nitrogen and a small blood supply, whereas the fastest tissues would have a small capacity for storing nitrogen and a great blood supply. *Boycott et al.* assumed that the 75 minute tissues were composed mainly of fat and that the 5 minute tissues of the body behaved much like water with respect to their solubility for nitrogen.

While the above hypothesis has, on the whole, been satisfactory in its application to diving on air, the advantageous effects of helium as a substitute for nitrogen in breathing mixtures, has led to the belief (*Sayers, Yant & Hildebrand*, 1924) that diffusion from one tissue to another, especially in the faster tissues has considerable influence on gas elimination.

When trying to analyze the mechanism of gas uptake and elimination by a certain bulk of tissue, there are *a priori* at least two factors, assuming respiration and cardiac output to remain constant, which govern the saturation or resaturation half-time for a certain non-reactive gas: (1) gas solubility in the tissue (capacity of the tissue for storing the gas) and (2) effectiveness of gas transportation to or from the tissue. It is obvious that, if a tissue is continuously and constantly perfused by blood, supposing the gas to be carried away at a certain rate (cc/minute), the time required for elimination is longer the greater the gas content of the tissue, i.e., storing capacity of the tissue for the gas in question. If different gases are compared in the same bulk of tissue, the storage capacity is proportional to the solubility coefficients for the gases in the tissue. At the same time the period for gas equilibration between tissue and blood is shorter the better the gas transportation.

The desaturation half-time or the time required for reduction of absolute gas partial pressure to 50 per cent in an arbitrary bulk of tissue may be derived as follows: Let P_t be the pressure in the tissue after the time, t, and P_o the tissue-lung pressure difference at the beginning of the

elimination, then

$$P_t = P_o e^{-kt}; \qquad (2)$$

Now if x equals the percentage of saturation in time t_x,

$$x.P_o = P_o e^{-kt_x};$$

$$t_x = \frac{e}{k} \log \frac{1}{x};$$

For x = 50 per cent:

$$t(\text{half-time}) = \frac{e}{k} \log \frac{100}{50} = \frac{1}{k} \cdot e \cdot \log 2;$$

$$\frac{e \cdot \log 2}{k} \qquad (3)$$

For obtaining a substitution for k, the time constant, the following general consideration may be applied: Let R be the rate of elimination of (cc of gas per minute), then

R = P.C. (in which P is the tissue-lung pressure difference, and C is a symbol for the effectiveness of gas transportation; the constant is omitted), and since

$-dA = R\,dt$ (in which A is the original amount of gas present in the tissue; $-dA$ denotes the amount eliminated in the time, t)

$-dA = P.C.dt;$

However, A = P.S. (according to Henry's law; S = coefficient of solubility), and therefore

dA = S.dP, so that the differential equation, which defines the interdependence between pressure and time, will be

$$S.dP = -P.C dt \text{ or } \frac{dP}{P} = -\frac{C}{S} dt;$$

Integrating with Z as the constant of integration:

$$\ln P + Z = -\frac{C}{S} \cdot t;$$

At the time t = O the tissue-lung gas pressure difference was P_o, so that

$$\ln P_o + Z = O \text{ or } Z = -\ln P_o;$$

Therefore

$$\ln P - \ln P_o = \ln \frac{P}{P_o} = -\frac{C}{S} \cdot t;$$

Accordingly

$$P_t = P_o e^{-\frac{C}{S}t} \qquad (4)$$

Hence, we have from equations (2) and (4) that $k = c.\frac{C}{S}$ (in which c is the constant that was omitted above.

Considering now equation (3), the desaturation of half-time was found to be $= \frac{1}{k} \cdot e \cdot \log 2$; therefore the desaturation half-time is also proportional to the solubility coefficient of the gas in the particular bulk of tissue, and inversely proportional to the effectiveness of gas transportation from the tissue. The half-time for equilibration between gas partial pressures in the lungs and in a certain bulk of tissue may therefore be expressed as:

$$T = c \cdot \frac{S}{C} \qquad (5)$$

where T = the equilbration half-time
c = a constant
S = the solubility coefficient for the gas in the tissue, and
C = symbol for the effectiveness of gas transportation to or from the tissue.

Perfusion versus diffusion. Theoretically, two factors will participate in the effectiveness of gas transportation, viz., blood-tissue perforation rate of the tissue (volume blood per volume tissue per minute), and rate of gas permeation within the intervascular spaces of the tissue. If diffusion or a permeability factor determined gas exchange, it would be expected that the equilibration half-time would be influenced by the predicted diffusion rate of the dissolved gas, which according to Graham's law is proportional to the reciprocal of the square root of the molecular weight. In the dual mechanism which may thus be theoretically assumed to determine the effectiveness of gas transportation, there are two anatomical possibilities: (1) if, in a certin bulk of tissue, the ratio of the surface of the capillary bed to the volume of tissue supplied by the vessels is high (high vascularization), the subsequent high blood-tissue perfusion rate may well mask differences in diffusion properties of inert gases, half-times for different gases in the tissue varying only as determined by the solubility coefficients; (2) in the case of a poorly vascularized tissue, there may be assumed to be for each active capillary a large active tissue volume immediate to the capillary in which diffusion

is rapid and equilibrium with blood gases is extremely rapid, and beyond this peri-capillary space an ultra-peri-capillaric space, in which gas exchange would be limited by diffusion and would follow the blood more slowly. For such types of tissue, equilibration half-times of different gases should vary as determined by solubility coefficients plus molecular weights, the latter affecting the permeation component in the gas transportation.

It is generally held that tissues, with the exception of fat, take up gases in proportion to their water content (*Campbell & Hill,* 1931). Theoretically then the body-exchange curve, representing the rate of uptake or elimination by the body as a whole, is the sum of an infinite number of exponential curves with different half-times, each representing tissue regions with the same individual ratio of fat-fluid content (average solubility coefficient) to efficiency of gas transportation (blood-tissue perfusion and diffusion rates). It is clear, therefore, that when trying to predict the half-time for any inert gas on the basis of an assumed half-time for nitrogen referring to a certain type of tissue, the calculation may yield several different half-times. Thus, some of the tissues assumed to have a nitrogen half-time of 40 minutes may be rich in fat and have an efficient gas transportation, and some may show the opposite properties. Hence, in the former case helium, having a very low solubility in fat compared to that of nitrogen, will yield a much shorter half-time than in the second type of tissues. This differentiation of an amount of tissue defined by a nitrogen half-time of 40 minutes into several types of tissue having different half-times when another gas is substituted for nitrogen, is in accordance with the results of *Jones, et al.* (1945), which appear to support in principle the thesis that the varying decay terms (e^{-kt}) of the component exponential expressions are not to be referred to anatomically defined phases.

The role played by diffusion in the blood-tissues gas exchange has been investigated by *Jones et al.* (1945). The technique employed involved the use of the radioactive inert gases A^{31}, N_2^{15}, Kr^{80}, Xe^{141}, and the nonradioactive gases helium, nitrogen, and krypton. Hence, together with the radioactive and non-radioactive technique, they had at their disposal for the study of inert gas exchange, gases with the molecular weight of 140 for the case of radioactive xenon to the molecular weight of 4 with helium. The intrinsic diffusion rates of these gases in isotonic salt medium were measured and found to follow Graham's law within experimental error. Comparisons of the gas exchange curves of N_2, A, He, and Xe, however, showed that regardless of the inert gas used (He to Xe), the time constants in non-fatty tissues of the gas exchange rate curves (cf. equation 1) are the same for all inert gases for a given individual under given conditions. The amounts of any gas involved in each component can therefore be predicted on the basis of solubility of the gas from measurement of one gas. The results leave no alternative other than to consider diffusion and transcapillaric permeability as being factors not limiting the gas exchange rate. Aside from the matter of differential solubility, the limiting factor of gas exchange is the blood-tissue perfusion rate of the body tissues. This must imply that the diffusion rates of the dissolved gases are very rapid over such barriers as may exist compared to the rate of movement of blood through the capillaries. Each gas, then, is exchanged at similar rates in the body tissues which are devoid of fat. In fatty tissues the exchange rates differ from the blood-tissue perfusion rate by a factor of the ratio $\frac{\text{blood solubility of the gas}}{\text{tissue solubility}}$ concerned. In the light of these measurements of gas exchange the beneficial effects of helium in the prevention of decompression sickness are not so easy to analyze, since the gas exchange rate of helium in the body is accordingly not influenced by the great diffusion rate of helium. Helium exchange is the same as nitrogen exchange except as regards fatty tissues. In view of the low fat solubility of helium, an exposure

to helium, with which fat is saturated more rapidly than with nitrogen, might make this tissue somewhat more prone to be in a critical state of supersaturation under certain combinations of compression exposures and decompression rates. *Behnke & Willmon* (1941) found that at a given pressure the tissues of the body will absorb about 40 per cent as much gaseous helium as nitrogen, and that the time for the elimination of the absorbed helium is about 50 per cent of the time required for nitrogen elimination. The latter result may seem hard to explain when considering the exchange rate of a gas in a tissue as determined by its solubility in the tissue. If it is the high solvent capacity of body fat for nitrogen that delays the elimination of this gas (*Behnke, Thompson & Shaw,* 1935), then the time for helium elimination should be shorter than 50 per cent, since the solubility coefficients for helium and nitrogen in fat at 38°C are 0.015 and 0.067 respectively (ratio = 1:4:5). However, some of the slow tissues may be characterized more by a poor blood-tissue perfusion rate than by high fat content, differences in fat solubility of the gases thus having less influence on the elimination times. It may also be assumed that in the "super-slow" tissues diffusion plays a role for the gas exchange.

Hydrogen as compared to nitrogen and helium. From the findings of *Jones et al.* it may be inferred that the very great diffusion rate of hydrogen as compared to that of nitrogen has no influence on the uptake or elimination of half-times. For the prediction and comparison of equilibration half-times for nitrogen, helium, and hydrogen, the solubility coefficients for the body tissues should be considered together with the blood-tissues perfusion rates for these tissues. Below is a table of solubility coefficients of the three gases in water and olive oil:

	Solubility at 38° C	
	Water	Olive Oil
H_2	0.017	0.036
He	0.009	0.015
N_2	0.013	0.067

It is obvious that from the point of saturation and desaturation half-times, the solubility characteristics of hydrogen are more favorable than those of nitrogen, but less favorable than those of helium. For further discussion of hydrogen half-times, see section on "Calculation of decompression tables and curves."

3. *Narcotic action*

The comparative narcotic effects of argon, nitrogen, and helium have been studied by *Behnke & Yarbrough* (1939) and *Behnke* (1940). In preliminary observations on the narcotic effect of krypton and xenon by *Lawrence, Loomis, Tobias & Turpin* (1945), definite central nervous system effects were described at gas pressures below one atmosphere. Reasoning from the Meyer-Overton hypothesis that anaesthetic effects are relative to the fat-water solubility ratio, the fact that argon has approximately twice the narcotic effect of nitrogen when breathed in equivalent concentrations, seems to be contradictory since the fat-water solubility of the two gases is nearly the same. However, xenon and krypton have fat-water solubility ratios of 20.0 and 9.6 respectively, and seem to have pronounced narcotic properties. Helium, the fat-water solubility ratio of which is 1.7, has been used in a simulated dive to 550 feet, and showed no narcotic effect. (*Behnke, End, & Brown,* 1945.)

The action of argon may indicate that the comparative solubility in oil (argon being twice as soluble as nitrogen) enters into the problem. Such a mechanism would explain also the narcotic action of xenon and krypton, as well as the non-narcotic property of helium.

Another physical property that might influence the narcotic activity of inert gases is their molecular weight. Helium, with a molecular weight of 4, induces the least disturbance, while the molecular weights of 28 and 40 for nitrogen and argon, respectively, indicate their relative difference in narcotic effect. Also the high molecular weights of xenon (131.3) and krypton (83.7) coincide with strong narcotic activity.

As to hydrogen, *Case & Haldane* (1941) have confirmed that the narcotic effect of air at high pressure (8.6 atmospheres) can be abolished by substituting hydrogen for nitrogen. Since the oil/water solubility ratio is 2.2, the comparative solubility in oil of hydrogen and nitrogen is 0.036 : 0.067, and the molecular weight of hydrogen is 2, there was reason to expect hydrogen to exert a very slight narcotic effect, comparable to that of helium.

4. *Resistance to inhalation*

As pointed out by *Kernan & Barach* (1937), Graham's law, postulating that the rate of diffusion of a gas is inversely proportional to the square root of the density, is applicable to the problem of breathing resistance of gases since it also governs the rate of effusion, or the passage of a gas through small orifices. Further experimental confirmation has been given by *Behnke & Yarbrough* (1939). From this it may be inferred that hydrogen should yield less inhalational resistance than any other inert gas.

Calculation of Decompression Tables and Curves

When attempting to determine the half-times for a certain non-reactive gas from its solubility coefficients for water and fat, and from the nitrogen half-times, it would seem simplest to obtain the new half-times from a comparison between the solubility coefficients of the two gases, considering the half-times for any inert gas in an anatomically defined tissue region as being proportional to the solubility coefficients of the tested gases (equation 5) under the assumption of an unchanged blood-tissue perfusion rate. However, the different kinds of arbitrary "nitrogen tissues within the same half-time class may well have different fat-fluid ratios and blood-tissues perfusion rates, although the average solubility coefficient $\frac{\text{blood-tissue perfusion rate}}{\text{ratio}}$ is constant. Thus tissues showing the same half-time for nitrogen may theoretically be either: (1) rich in fat and well perfused or, (2) devoid of fat and poorly perfused. Now if, for instance, helium is substituted for nitrogen, the classification which is a physiological rather than an anatomical one, may become deranged, and new tissue combinations will arise with common half-time for this gas. This is because helium will cause considerable shortening of the half-times for highly vascular fat-rich regions compared to those of non-fatty poorly perfused regions within the same nitrogen half-time groups. Theoretically the anatomical arrangement of the different groups will remain unchanged from one gas to another only for gases with the same fat-water solubility ratio. Thus, it would be possible to calculate the half-times for argon, showing the same fat-water solubility ratio (5, 2) as nitrogen, simply by multiplying the numbers 5, 10, 20, 40, and 75, which are the half-times for the arbitrary "nitrogen tissues," by the factor 2, which is the ratio of argon-nitrogen solubility coefficients, for water (0.026 : 0.013) as well as for olive oil (0.14 : 0.07).

In the case of hydrogen (as compared to nitrogen) the separation and reclassification of certain fat-rich regions into classes with a shorter half-time than yielded by the remaining bulk of tissue in the same nitrogen half-time category should be slightly less accentuated than for helium. The olive-water solubility ratio for helium is 1.7, for hydrogen 2.1 and for argon and nitrogen 5.2. Therefore, a simple calculation of hydrogen half-times by using the nitrogen half-times multiplied by a solubility factor—as in the case of argon—is not justified theoretically.

The fact that there is little reason to conceive any anatomical identity between nitrogen and hydrogen half-time regions renders the computation of decompression tables and curves for hydrogen from nitrogen half-times ambiguous. However, for practical purposes the differentiation of body tissues into five categories with varying hydrogen half-times seems to be as justified as is the assumption of five different nitrogen half-time tissue regions.

Owing to the lack of data as to the rate

of elimination and uptake of hydrogen by the body, the approach to the problem of determining decompression rates had to involve certain assumptions. The consideration of solubility properties of hydrogen as compared to those of nitrogen made it probable that the slowest hydrogen tissues should be considerably faster than the nitrogen 75-minute tissues. On the other hand, the fastest hydrogen tissues should have about the same half-time as the fastest nitrogen tissues because of the similarity of solubility coefficients for aqueous tissues.

The degree of supersaturation allowed in the calculation of decompression rates was fixed at the ratio 1.7 to 1 for all tissues, although ratios as high as 5.5 to 1 have been applied to rapidly desaturating tissues and as low as 1.7 to 1 only for the slowest desaturating tissues (*Hawkins, Schilling & Hansen,* 1935).

From the results of decompression experiments on rats and cats in a small decompression chamber and from discussions of the various factors which could be assumed to be involved in the uptake and elimination of gaseous hydrogen by the body, a computation of decompression tables and curves for divers was made by Professor *Zotterman* including depths of 70, 90, 100, 110, 140, and 160 meters. In these calculations the rate of gas exchange in the fastest tissues was assumed to be dependent—apart from the factor of solubility—mainly on the effectiveness of blood perfusion, whereas the exchange rate in the slowest tissues, the role of diffusion in the body gas exchange being incompletely known at the time, was believed to be influenced to a certain degree by the very great diffusion velocity of hydrogen. After introducing into the calculations the solubility coefficients of hydrogen for body fluids and fat as compared to those of nitrogen (see above), five types of tissue with the hydrogen half-times of 5, 9, 15, 20, and 25 minutes were assumed to represent the hydrogen gas exchange rate of the body as a whole. Thus the slowest hydrogen tissues were assumed to be considerably faster than can be anticipated from a mere comparison between nitrogen and hydrogen solubilities in fat. Starting from the hydrogen half-times thus assumed and from an allowed supersaturation ratio of 1.7 to 1 for all tissues, the method described by *Momsen* 1942 was used for calculation of decompression tables. Thus the percentage saturation or desaturation of each type of tissue at the ambient water pressure was calculated as a function of the time unit. This procedure yielded the partial pressures of hydrogen and nitrogen directly in atmosphere (absolute pressure) in the five types of tissue, and for each type the sum of these pressures was not allowed to exceed 1.7 times the ambient absolute pressure. The partial pressures of hydrogen and nitrogen in each type of tissue as well as their sum were usually graphically represented as plotted against time, an example of which is shown in Fig. 1.

From what has been mentioned above it is highly dubious whether it should be considered theoretically correct to add hydrogen and nitrogen partial pressures within each of the assumed five tissue types, since to a certain extent the corresponding hydrogen and nitrogen half-time tissues are most probably not anatomically identical. However, no other basis for calculation of the combined pressure was found more acceptable, and it may at least be assumed that this method of calculation will give a rough average of pressure changes in the tissues during a dive which involves a substitution of hydrogen for nitrogen and vice versa during the descent and ascent respectively.

The Practical Testing of the Method

The hydrogen method has been tested in the open sea during four descents to the depths of 40, 70, 110, and 160 meters respectively. The descents were all made by *Arne Zetterström,* who originally suggested the method to the Royal Swedish Navy. The 40 and 110 meter dives involved the use of the so-called Zetterström synthetic gas mixture, which contained 72 per cent H_2, 24 per cent N_2, and 4 per cent O_2. The two descents

took place in the autumn of 1944, and were entirely successful. However, the synthetic gas mixture was abandoned, in spite of the advantages in its production, mainly because the pure 4 per cent O_2 in H_2 mixture offers a lessened inhalational resistance and shorter decompression times.

The 70 and 160 meter dives were made in the summer of 1945, on which occasions the 4 per cent O_2 in H_2 mixture was employed. The 70 meter dive was made according to plan and was successful. The diver reported that the inhalational resistance was conspicuously slight and that no ill effects from the inhalation of hydrogen had been experienced. The diver had to use Morse code at greater depths because the voice became nasal and indistinct owing to the high speed of sound in hydrogen. He felt the low temperature of the water sooner because of the high heat conductivity of hydrogen gas. Preheating of the gas is therefore desirable.

During this last diving experiment *Zetterström* was accidentally killed as mentioned in a preceding article of this issue. However, he safely reached the depth of 160 meters and reported that no sign of narcotic effect was noticed, and that the in-

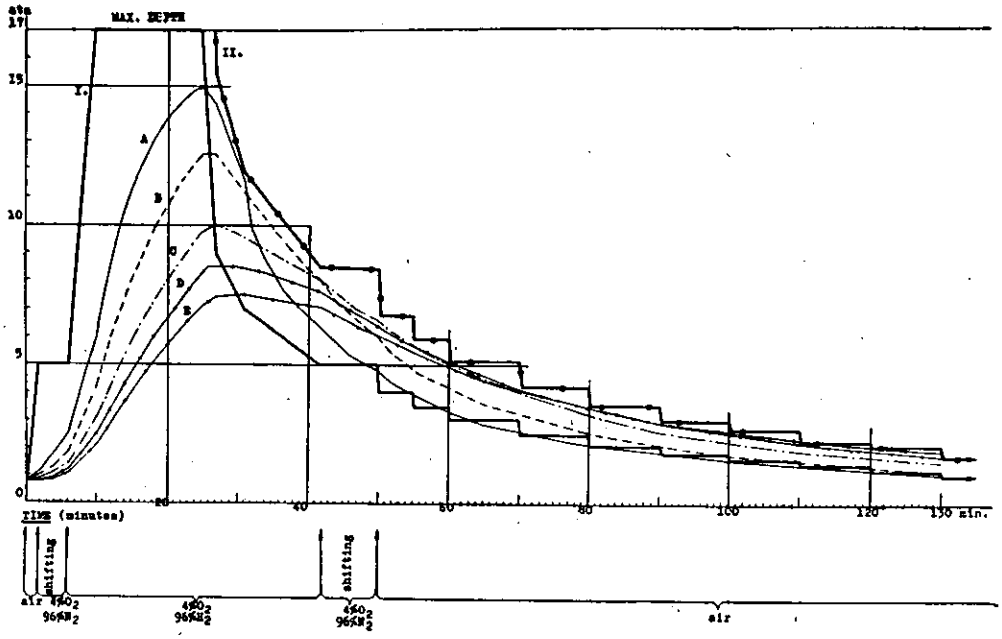

FIG. 1. *Graphic representation of decompression procedure from a dive of 160 meters.*

The curves are calculated on the following assumptions:

1) Rate of descent = 30 meters/minute.
2) At 40 meters (5 atmospheres absolute) 4 mins. stop for shifting from air to intermediate mixture of 4 per cent oxygen in nitrogen.
3) Subsequently breathing of 4 per cent oxygen in hydrogen is started.
4) Maximal depth 160 meters (17 atmospheres absolute).
5) When ascending the diver at the 40 meters stop once more breathes intermediate mixture of 4 per cent O_2 and 96 per cent N_2 for 4 minutes and then, on his way to the surface, air.

Legend:

I (Continuous thick line): actual ambient pressure
II (dotted thick line): limit of supersaturation
A-E (thin lines): partial pressures of $H_2 + N_2$ in tissues halfsaturating in 5, 10, 20, 40 and 75 mins. respectively.

halational resistance was no greater than with ordinary air at 40 meters. No ill effects from the hydrogen were reported.

Summary

The background of the Zetterström hydrogen deep-diving method as developed and practiced in the Royal Swedish Navy is given.

The theoretical properties of hydrogen as a substitute for the nitrogen of the air for diving purposes are discussed. Comparisons between nitrogen, hydrogen, helium and other gases are made with respect to gas uptake and elimination, narcotic effect, and inhalational resistance.

The basis for the calculation of hydrogen half-times and decompression tables and curves is discussed.

Practical diving experiments in the open sea with hydrogen deep-diving method are reported.

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Anesthetic Action of Inert and Unreactive Gases on Intact Animals and Isolated Tissues[1]

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ALTHOUGH many investigators have been concerned with the depressant actions of inert gases upon the intact organism, there have been relatively few studies of their effects on isolated tissues (1, 2). Haywood was unable to detect any change in the cleavage time of arbacia eggs after exposure to 61 atm. of nitrogen, while Marshall found no functional alteration in the beating turtle auricle or frog nerve-muscle preparation after saturation with nitrogen or helium at 82 atm., (3, 4). On the other hand, South and Cook (5) have reported an increase in the rate of oxygen consumption by mouse liver and brain slices in the presence of less than one atmosphere of argon, xenon or helium.

The central nervous system depressant action on mice has been extended from an earlier study to 11 gases that act in the absence of chemical bonding under the conditions encountered in the body environment (6). Present information suggests that they are completely eliminated by the lungs unchanged from the form in which they were absorbed (7).

To measure the effect of these agents upon isolated tissues, mammalian peripheral nerve has been used since one may anticipate a parallel in their action on this excitable structure and the depression already demonstrated in the intact animal. To this end several criteria may be utilized to advantage with peripheral nerve, viz.: decrease in excitability, blockade of fiber conduction and alteration in the polarized state of the constituent fiber membrane. Wright has shown that narcosis of mammalian nerve produced by alcohol and ether vapor is attended by a change in these electrical properties(8).

METHOD AND RESULTS

Intact Animal Studies. To measure the depressant effect of inert gases relative to one another the pressure required of each to protect 50% of a group of mice from electroshock convulsions was determined (ED_{50}). Twenty to thirty animals were tested at five different pressures of each gas and the results plotted with respect to the percentage protection afforded on logarithmic probability paper, (6). In the case with helium, however, only a single point was secured, affording 0% protection at the maximum pressure attainable of 100 atm. By extrapolation to probit 5 from this point, representing 30 animals, with a slope similar to those obtained with other gases, an ED_{50} of 163 atm. can be predicted for helium. The true ED_{50} is probably greater than this depending upon the reliability of this single point.

Isolated Tissues. Sciatic nerves from adult albino rats weighing 300–400 gm were dissected free of adjoining tissue and placed in oxygenated Ringer-Tyrode solution for 1 hour. For stimulating and recording purposes the nerve was drawn through four Ag-AgCl electrodes mounted in a leucite trough enclosed in the high pressure chamber with one atmosphere O_2 present at 35–37°C. The action potentials resulting from periodically applied stimuli of .2 msec. duration were amplified to provide an oscilloscope tracing for direct measurement of the spike complex and for recording on film. The gases were admitted slowly into the chamber until it became apparent that the action spikes were 90–100% diminished in amplitude. To avoid overshooting the blocking pressure a period of at least 30–40 minutes elapsed before further addition of a particular agent. Pressures in excess of those available in commercial cylinders were supplanted by diminishing the volume of the vessel with glycerin forced in with an hydraulic pump. When the measurements were completed the gases were slowly expelled to observe the reappearance of the action potential as a control measure. Throughout the blockade experiments supramaximal shocks were applied since the threshold of excitation was always found to increase as the narcosis progressed toward complete extinction of the conduction process. About 20–30 minutes were required at any pressure for the nerve trunk to reach equilibrium by diffusion with the surrounding gas phase. Evidence that this period is related to physical saturation and

Received for publication March 29, 1954.

[1] These studies were supported by a contract between the Office of Naval Research, Department of the Navy, and The University of Rochester, and a grant from the Public Health Service.

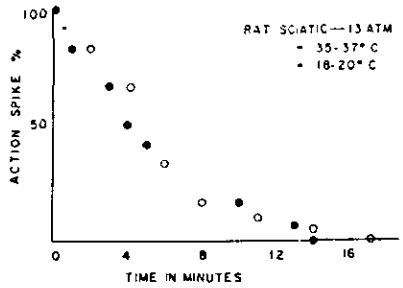

FIG. 1. *Ordinate:* the height of the recorded action potential resulting from the application of supramaximal stimuli expressed in per cent of the control. *Abscissa:* time in minutes after the introduction of N_2O just sufficient to block conduction. ○ Chamber temperature 35–37°C. ● Chamber temperature 8–20°C.

is not of a chemical nature can be seen by reference to figure 1, where the time course of fiber blockade was measured in the same nerve trunk and found to be almost identical at two widely differing temperature ranges.

It was not surprising to find that some preparations were more resistant to narcosis by the gases than others, thus a small range of blockade pressures (B.P.) was obtained for each. Alteration in the degree of polarization produced by the gases on rat nerve was determined by the method employed by Lorente de No (9). An hour or two after one end of a nerve trunk was immersed in 0.11 M KCl and the other in Ringer-Tyrode solution, a demarcation potential of from 20–30 mv could be measured between the two solutions. When the potential difference reached its maximum the nerve preparation was secured in the pressure chamber. It was then possible to observe the effect of the gaseous agents on the remaining polarized segment of the nerve at concentrations known to cause suppression of fiber conduction. A permanent record of this electrical activity was obtained after proper amplification, on a recording galvanometer. Space limitations inside the chamber made it impossible to observe conduction blockade and depolarization simultaneously in the same preparation although independently the two processes required roughly the same time period.

The results of all the experiments are summarized in table 1. Included among several physical constants are the gas solubilities in olive oil at 37°C. Those values not available in the literature were determined by the author by the method described in Reilly and Rae, *Physical Chemical Methods*. In another column the thermodynamic activity of the gases at the ED_{50} pressure was calculated from the expression $a = f/f^{\circ}$, f being essentially the ED_{50} at 37°C and f° the fugacity of the substance at the standard state at (37°C) obtained from the vapor pressure by the principle of corresponding states (10). The fugacity term is used to relate the vapor pressure to ideal gas behavior by the approximation f°/P vapor = P vapor/P ideal (15).

DISCUSSION

In Figure 2A a correlation between ED_{50} pressure for each gas, expressed on a logarithmic scale, and their Bunsen coefficient in olive oil produces a fairly smooth curve which, according to finite differences, is best described as a rectangular hyperbola. For convenience, however, the same data have been plotted on a log-log scale in figure 3 for comparison with the other results. In the third column in table 1 is the calculated concentration of gas in moles per liter in a lipid phase at the site of action (11). Several assumptions are made in the calculation: *a*) that Henry's Law is obeyed at these low concentrations; *b*) that the gases behave ideally at these pressures; and *c*) that body lipids such as lecithin, sphingomylin, cholesterol, etc., behave like neutral fat molecules in their affinity for dissolved substances. The first and second assumptions are probably valid within the limits of error of these experiments, but it is difficult to justify the last since Kety found that the lipid fraction of brain does not dissolve as much nitrous oxide as would an equal amount of neutral fat (12). Similar conclusions for other anesthetic gases have been reported by others (13). The synapses of the central nervous system reside in the grey matter that contains only 4% lipid, while the white matter containing the fibers has over twice this amount. It is well known that synaptic transmission in the spinal cord is more susceptible to the effects of most narcotics than the conduction process in nerve fibers (14). The greater partition of the agents in this constituent of the nervous system would have little influence upon the function of the synapse itself.

There is little doubt that a clear relation

TABLE 1

Gas	ED_{50} Atm.	Olive Oil		f° atm. 37°C	a_{liq}	Fiber Blockade atm.	B.P., ED_{50}	Δ Demarcation Potential at B.P.
		Bunsen Coeff. 37°	Conc. M/l.					
Cyclopropane	0.045	7.15	.036	7.5	.0060	1.7–1.9	36	−10%
Dichlorodifluoromethane	0.26	5.1	.057	7.0	.037	3.4–4.7	18.5	− 8%
Ethylene	0.47	1.28	.026	49.	.0096	9.8–12.5	26	−12%
Xenon (1)	0.51	1.7	.038	52.	.0098	not determined		
Nitrous Oxide	0.58	1.6	.036	44.	.013	10–13	23	−19%
Krypton (1)	1.8	.43	.034	215.	.0084	not determined		
Sulphur Hexafluoride	1.87	.25	.020	20.4	.091	≫21†	≫11	
Methane	2.9	.28	.043	262.	.011	92–110	36	−16%
Argon	12.6	.14	.077	725.	.017	310–340	27	−11%
Nitrogen	18.0	.067	.052	1700.	.010	not determined		
Helium	>163.0	.015	>.107			*		*

* Control at 350 atm.: no observable change in action potential or demarcation potential.
† In excess of its vapor pressure at 25°C.
(1) Lazarev, N. (estimated ED_{50})

exists between narcotic activity and solubility in olive oil, figure 2*a*. Not only do the chemically unreactive gases like nitrogen, methane and sulphur hexafluoride fit in the curve rather well, but nitrous oxide, ethylene, dichlorodifluorimethane and cyclopropane also stand comparison with the noble gases in this figure. It seems unlikely, therefore, that a separate mechanism of action should be suspected for any one of them. Although a general theory of narcosis cannot be established from these findings, it is none-the-less possible to predict narcotic potency on a physicochemical basis adapted from the Meyer-Overton hypothesis.

According to Hildebrand (15) a fair estimate of the solubility of a gas in an ideal liquid at a given temperature may be calculated by the expression $X = 1\ p^\circ$, where p° is vapor or saturation pressure at this same temperature and X is the mole fraction dissolved at one atmosphere. Under the conditions of these experiments most of the gases are beyond their critical point and p° is impossible to measure directly. Extrapolation of the vapor pressure above the critical point with the Clausius-Clapeyron equation produces an imaginary but useful value for p° providing the heat term remains constant. In an ideal liquid, dilution and mixing of its molecules will be athermal without changes in volume. As the liquids depart from ideality, non-specific intermolecular forces and molecular volume effects will increase its internal pressure[2] and the solubilities of a series of gases measured in the liquid decrease from their ideal value of $X = 1/p^\circ$. The Bunsen solubility coefficients for benzene and other non-polar liquids closely parallel those listed in the table for olive oil. Apparently the same physical mechanisms which determine the extent to which gases will dissolve in a non-polar liquid also determine their Bunsen coefficient for olive oil; and if the internal pressure for this substance were known, a nearly absolute rather than a relative value could be predicted.

Reference to the column of thermodynamic activities or chemical potential at the ED_{50} reveals that this index of anesthetic potency is fairly uniform from one gas to another in so far as the f° term can be used to predict the solubility of a gas in a non-polar liquid or the Bunsen coefficient in olive oil, figure 2*b*. However in the case of CCl_2F_2 and SF_6, due perhaps to polarity or large molecule size, $1/f^\circ$ does not coincide with the real solubility because smaller amounts are dissolved, and their narcotic potency is not so accurately established by this means. For a discussion of the relation between chemical potential and narcotic activity in other substances the publications of Ferguson and Brink and Posternak should be consulted (16, 17).

Present knowledge regarding excitable tissues places much emphasis on the membrane

[2] Internal pressure $= (-E/V)^{1/2}$ where $-E$ is the energy of vaporization to the gas at zero pressure and V is the molal volume of the liquid.

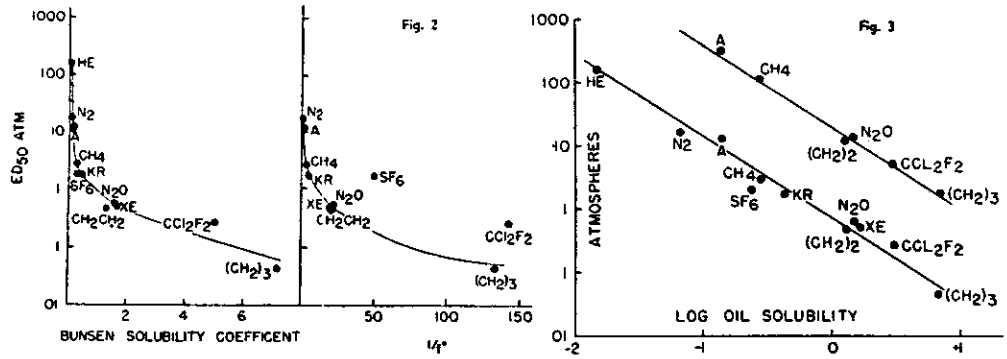

FIG. 2. *Left ordinate:* ED_{50} in atmospheres. *Left abscissa:* gas solubility in olive oil at 37°C expressed in cc/cc STP—Bunsen coefficient. *Right abscissa:* reciprocal of gas fugacity obtained from real and extrapolated vapor pressures at 37°C × 10^{-3}.

FIG. 3. Relation of ED_{50} pressures (*lower line*) to the pressures required for nerve fiber blockade in the rat sciatic (*upper line*). *Ordinate:* pressures in atmospheres. *Abscissa:* log of gas solubility in olive oil at 37°C expressed in cc/cc at STP—Bunsen coefficient.

that maintains between inside and outside of the cell a potential difference essential for impulse transmission. The behavior of this structure in the presence of narcotizing concentrations of gases is shown by the results obtained with fiber blockade and depolarization as observed in rat peripheral nerve, figure 1. While pressures required for block of conduction were always greater than for anticonvulsant action (ED_{50}), the fact that the ratio between the two is fairly constant suggests that the blocking mechanism in isolated fibers is the same as the central nervous system depression produced at the synapse, table 1, figure 3. In all cases reversible decrease in the demarcation or polarization potential of rat sciatic nerve followed exposure to gas pressures known to block conduction. In the final column of table 1 is the average depolarization in five to eight experiments caused by each of the gases when tested at their B.P. At pressures higher than were required for blockade reversible depolarization was always more extensive and occurred more rapidly.

While Wright found depolarization and cessation of conduction to occur simultaneously in alcohol and ether vapor (8) it remains doubtful whether the small magnitude of depolarization produced in these experiments is responsible for total fiber blockade. However, in the course of neuronal depression by the gases at their B.P. there was a definite interference with the polarization mechanism or with ionic movements across the fiber membranes. Lorente de No (9) has suggested the necessity for maintaining a critically polarized state of the membrane which is necessary for excitation and conduction but the findings of Bishop (18) and of Brink (19) would indicate that the two phenomena are probably unrelated since cocaine, amyl alcohol and chlorotone do not depolarize at blockade concentrations. In this respect it appears that these gases behave like veratrine, aconite, and excess K ions.

The results of Graham (20) who measured threshold changes in frog sartorius muscle in the presence of high pressures of nitrous oxide and ethylene indicate that much greater amounts of each are necessary to prevent conduction, as the experiments here demonstrate, than to diminish excitability of the contractile process.

With regard to the mechanism of action of noble and inert gases like argon, nitrogen and methane, as far as can be determined with a neurophysiological approach, there is little basic difference between the effects of these agents upon isolated nerve and the reported findings of others where ethyl alcohol, aconite, veratrine, etc., were used. Nevertheless, it is of considerable interest to know that these non-bonding agents are capable of the same specific functional alteration of the nervous and neuronal system as are narcotic agents without such properties.

These gases may produce narcosis like the barbiturates and chloretone by depressing

certain respiratory processes in nerve cells, specifically pyruvate or lactate oxidation (21). With xenon at less than 1 atm., Levy and Featherstone (22) were unable to alter the *in vitro* respiration and oxidative phosphorylation of guinea pig brain. However, one could anticipate a more generalized depression of isolated tissue activity if amounts nearer to the blockade pressure, figure 3, were employed.

SUMMARY

A comparison has been made of the central nervous system depressant action of 11 chemically unreactive gases with reference to the partial pressure of each that is necessary to protect 50% of a group of mice from electroshock convulsive seizures. At consistently higher pressures six out of seven of the gases tested diminish excitability, block conduction and produce significant depolarization of isolated rat peripheral nerve. The depressant action of these substances is fundamentally related to the facility with which they dissolve in olive oil or a non-polar liquid to produce a critical concentration of nolecules at their site of action. The relative solubility of a gas in olive oil or a non-polar liquid is inversely proportional to its standard state fugacity. For two gases of very high molecular weight, smaller amounts were dissolved than would be predicted by this rule and the relation between the depressant action of a gas and its fugacity is not so clear.

The author is indebted to Dr. E. B. Wright for his valuable assistance during the course of this work and to Dr. Frank Brink for his comments on the manuscript.

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Reprinted from the Proceedings of the NATIONAL ACADEMY OF SCIENCES
Vol. 48, No. 6, pp. 1008–1014. June, 1962.

*THE AFFINITY OF NARCOTIC AGENTS FOR INTERFACIAL FILMS**

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Communicated by Julius H. Comroe, Jr., April 12, 1962

Although investigators have suggested for many years that inert gases cause narcosis by acting on the lipid-containing membranes of excitable cells, a direct demonstration of this localization has not been forthcoming. In contrast, Pauling[1] has recently suggested that inert gases induce narcosis by seeding aqueous clathrate microcrystals in cells, which impede the ion movements that are thought usually to accompany excitation. In support of this idea he has shown that the anesthetic potency of inert gases is systematically related to the stability of their clathrates and to the electronic polarizability of their molecules or atoms. He refers to the cellular lipids as insulators and suggests that they are not primarily involved in narcosis. Miller[2] has also recently suggested that inert gases produce narcosis by forming hydrates not necessarily in strictly stoichiometric proportions, i.e., "icebergs," with the water in or around excitable cells. Both authors mention the instability of such complexes at 37°C and invoke the cooperation of materials intrinsic to the organism to explain structuring of water to a significantly increased degree at partial pressures of inert gases which actually cause narcosis. Miller suggests that "iceberg" formation may occur particularly at interfaces and alter the physical state of membranes, decreasing their electrical and chemical reactivity. For example, if it is assumed that a free energy of activation determines penetration through a nerve membrane and contiguous material and thus regulates excitability,[3] then the action of the narcotic might be described as increasing this

activation energy and preventing excitation when the agent is present in sufficient amount.

Because of our interest in interfacial films as models of cellular membranes and because of the large body of evidence relating the processes of excitation to alterations in the properties of lipoidal membranes, we have done experiments to determine how strongly inert gases interact with surface films on water. This information might permit a judgment on whether such interactions occur to a significant extent at cellular interfaces, and is the basis for this preliminary report.

We spread films on distilled water at room temperature (24–25°C) in a teflon trough enclosed in a plexiglas chamber and measured surface tension with a platinum plate hanging from a strain gauge. A current of air saturated with water vapor at room temperature passed slowly over the surface of the trough. We added sufficient material to the surface to lower surface tension 2–10 dynes per cm. In this range, the initial value of tension had little effect on the results. After the tension stabilized, a mixture of gases containing an anesthetic, saturated with water vapor, and equilibrated to room temperature, was passed over the surface until the surface tension was steady. When air was again passed over the trough, surface tension returned to its initial value. This sequence could be repeated many times in several hours and gave reproducible results. Although we actually measured changes in surface tension, we prefer to express them as changes in film pressure, especially since inert gases can lower tension much more when a film is present than when the surface is very clean (Fig. 4). We did initial experiments with films of pure stearic acid, cholesterol, or synthetic lecithin, and the results were similar to those given below. Later experiments were done with films of a complex lipoprotein extracted from beef lung[4] because we think its composition is closer to that of cellular membranes.

Table 1 gives the results of a single sequence in which six gases were presented in

TABLE 1

EFFECT OF SIX NARCOTIC GASES ON SURFACE TENSION OF LIPOPROTEIN-COVERED WATER AT 25°C*

Gas	Partial pressure (mm Hg) applied	Fall in tension (dynes per cm)	Pressure (mm Hg) for 0.39 dynes per cm
N_2O	589	0.49	470
C_2H_6	736	4.3	67.0
CH_3I	405	20.4	7.7
C_2H_5Cl	736	23.8	12.0
$CHCl_3$	205	26.0	3.1
$CF_3CHClBr$	295	36.0	3.2

* Lipoprotein added to reduce surface tension of distilled water by seven dynes per centimeter.

order of increasing effect. Each gas was purged from the system with flowing air, and surface tension returned to the initial value before the succeeding gas was admitted. Each agent having a vapor pressure less than one atmosphere was presented in air saturated both with water vapor and with the agent at room temperature.

We calculated from our data that the quantity of nitrous oxide sorbed in the interface at the narcotic partial pressure for mice determined by Carpenter,[16] is 1.6×10^{-11} mole per square centimeter. Since the sorption-vapor pressure curves are linear in the ranges of partial pressure actually used and the rise in film pressure is proportional to the number of agent molecules sorbed per unit area of surface,[5] we

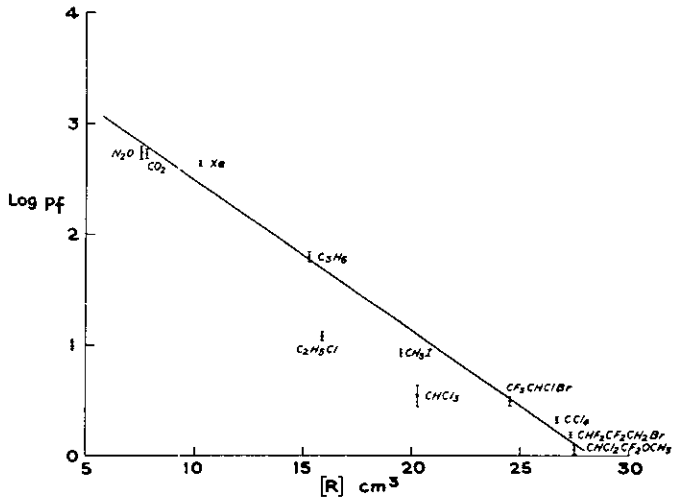

FIG. 1.—Vertical lines indicate an average deviation above and below mean pressure. CO_2 effect was measured on 0.01 M H_3PO_4, pH 2.4, to suppress its ionization. Other nonionic agents gave the same results on this substrate as on distilled water. Pressure in millimeters of mercury.

interpolated from our observed effects the partial pressures of the other agents in equilibrium with 1.6×10^{-11} mole of sorbate per square centimeter. Figure 1 shows these equilibrium pressures plotted against the molar refractions of 11 agents, varying over a potency range of about 500-fold. The points falling farthest from the curve represent compounds that are known to have significant dipole moments. Measurements of dipole moment are available for CH_3I, C_2H_5Cl, and $CHCl_3$, and when a rough correction to their total polarization is made, assuming an average field strength of 8×10^5 volts per centimeter in the interface, their points fit the curve (Fig. 2) somewhat better.

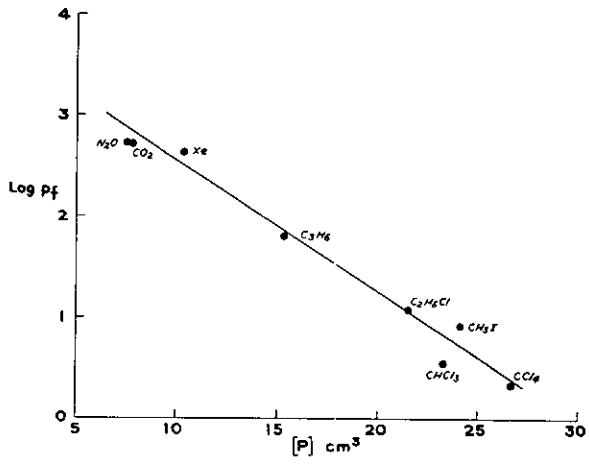

FIG. 2.—Molar polarization of agent corrected for effect of interfacial field. Pressure in millimeters of mercury.

In Figure 3 the partial pressures required for anesthesia are plotted against the partial pressures calculated to be in equilibrium with 1.6×10^{-11} mole of sorbate per square centimeter at 25°C. There is a systematic relationship between anesthetic potency of an agent and its affinity for the interface.

We believe that the data presented above permit us to conclude that inert gases can interact significantly with the interfacial lipoprotein of living cells. For example, the nonpolar substance carbon tet-

rachloride at a partial pressure of 100 mm Hg raises film pressure 18 dynes per centimeter (roughly 36 atmospheres, assuming that the pressure is "uniform" throughout the film and that the film is about 50 Å thick), and even xenon at 736 mm Hg raises film pressure 0.66 dyne per centimeter (1.3 atmospheres). Since the composition and structure of cellular membranes and of the experimental films are very similar, it would seem reasonable to think that these agents are also sorbed into the cellular interfaces, where they may change the effective dielectric constant and permeability. Such sorption may also alter critical structural relationships in those enzymes supporting oxidative phosphorylation and electron transport which probably reside in the lipoprotein complex of mitochondrial membranes. The changes in cellular permeability, excitability, and metabolic activity caused by inert gases would seem to be explained at least as well by this hypothesis as by the theory of hydrate formation.[1, 2] Changes of state in the interfacial region have been demonstrated in reversal of emulsions by inert gases and divalent cations,[6, 7] in the action of local anesthetics[8] and veratrum alkaloids[9] on lipid monolayers, and in the reversible liquefaction and solidification of fatty acid films competitively by mono- and di-valent cations.[10] Changes of state are also seen in the swelling of mitochondria and uncoupling of oxidative phosphorylation induced by nonpolar substances[11, 12] and in the antagonism between calcium and magnesium ions in this regard.[11] We believe it is likely that inert gases act on excitable cells by causing similar changes of state in their membranes.

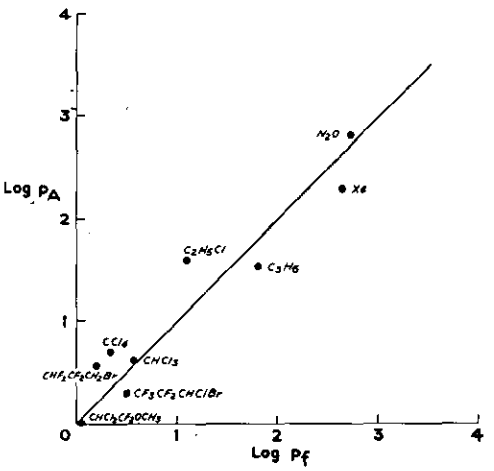

FIG. 3.—Abscissa, partial pressure of agent in equilibrium with 1.6×10^{-11} mole of agent per square centimeter of interface. Ordinate, partial pressure of agent for anesthesia in mice. Pressure in mm Hg.

From a more nearly operational point of view, we can express our results in this general statement: inert gases at partial pressures sufficient to bring about a standard effect in a biological system act on a lipoprotein-water interface to cause a standard decrease of 0.39 dyne per centimeter in the interfacial tension. This effect corresponds to the addition of less than 1 per cent to the mass of the interfacial region and, as force-area isotherms at high film pressure show, the agents do not displace film material from the surface. Since the area, temperature, and volume of the interfacial region are substantially constant, this effect corresponds in turn to a decrease of 0.39 erg per square centimeter in the differential free energy of the interface. It can be visualized as a tendency to expand the film, to replace water in the interface, or to reduce the energy of the interface by interaction between water and the agent, or by a combination of these processes.

The lack of quantitatively similar changes in the absence of a surface film (Fig. 4) is not consistent with the idea that the interaction occurs solely with water. The necessity for a film suggests that the interaction occurs with the film or that the

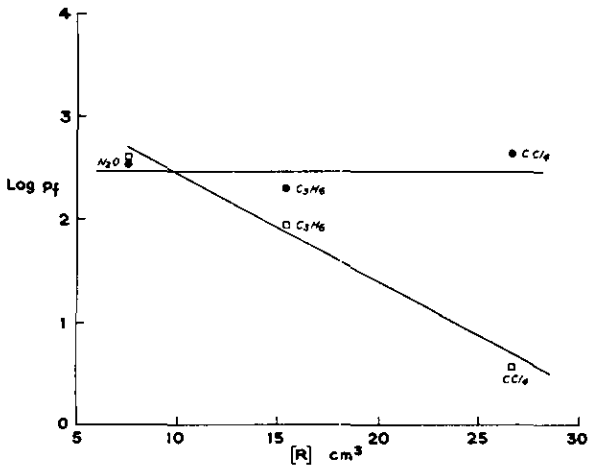

FIG. 4.—Effects of agents whose dipole moments are known to be small, on clean water and on water with protein film containing very little lipid. Pressure in millimeters of mercury. Circles, water. Squares, film surface.

film makes possible a significant interaction between agents and interfacial water, or both. The effect does not require a lipid surface film. Figure 4 shows that it occurs, but to a lesser extent, with a highly hydrated film of defatted plasma albumin. Almost identical results were obtained with a film of crystalline ribonuclease. This effect is probably due to the interaction of agents with the hydrophobic side chains ("lipid parts") of these proteins but could imply that at least part of the interaction occurs in water structured by the film. Thus, the quasicrystalline state of even a liquid surface film may provide the restraints necessary to stabilize water-narcotic complexes. Since cellular membranes are rich in lipid and since lipid films enhance the interfacial interaction very strongly, it is reasonable to think that the effect of nonpolar agents is greatest at the membranes. In this view, the difference between hydrate and lipid theories of inert gas narcosis becomes indistinct and the essence of the reaction would seem to be the formation of lipid-protein-water-agent "complexes" in cellular membranes. This hypothesis at once suggests how the chemical and electrical reactivity of excitable structures may be decreased by inert gases. Either the replacement of water in the interface by nonpolar agents or the stabilizing of water-membrane complexes by such agents would be expected to increase the free energy of activation for passage of material through the interface and thus to impede depolarization. This description likens the membrane to a semiconductor in which current flow depends on the "activated formation of holes" and in which altering the composition of the semiconductor can modify the energy of "hole" formation and vary its resistance. (Incidentally, a mechanism for cold anesthesia follows directly from this description.) Such considerations are also related to theories of permeation through monolayers and to the dependence of permeability on film pressure in solid films or on film viscosity in liquid films.[13-15]

In addition, such a description is consistent with the experimental observation that inert gases, like local anesthetics of the cocaine type, block nerve conduction without depolarizing the membrane. An interesting comparison can be made between the number of gaseous and the number of crystalloidal narcotic molecules sorbed per unit area of interface when the agents are presented at minimum blocking concentrations. Using published partial pressures for conduction block in the rat sciatic nerve[16] in conjunction with our data for sorption of gases into the lipoprotein-water interface, we calculate that 18.6×10^{13} gas molecules are sorbed

per square centimeter at the blocking pressure, corresponding to a change of 7.7 dynes per centimeter in film pressure. Skou's data[8] show that an average of 8.7 $\times 10^{13}$ local anesthetic molecules are sorbed per square centimeter of lipid-water interface at the minimum concentrations for blocking conduction in the frog sciatic nerve, and correspond to an average change of 6.9 dynes per centimeter in film pressure. Thus, the *in vitro* surface concentrations and effects of two very different types of agents are similar when they are presented to a lipid-containing interface at concentrations which give similar biological effects. Like the inert gases, the local anesthetics act much more strongly at a lipid-containing interface than at the clean-water surface.[8] In this instance too, the correlation between the behavior of the biological system and the interfacial model is improved when the latter contains lipid, suggesting once more that the biological effects of narcotics are enhanced at lipid-water junctions, such as cellular and subcellular membranes, and that even a nonspecific theory of narcosis should rest at least in part on the properties of lipids.

The energy of sorption of inert gases *in vivo* and *in vitro* deserves some comment. In neither case do we know the thermodynamic activity of receptor material or of receptor-narcotic "complexes," but since equilibrium with the agents is brought about, and since none was used at a "nonideal" pressure, ratios of agent activities can be taken as the ratios of their effective pressures. On the reasonable assumption that receptor and complex activities are identical for a given effect either *in vivo* or *in vitro*, though not necessarily identical in both systems, the differences can be calculated from $\Delta\ (\Delta F^\circ) = -2.3RT \log_{10} P_1/P_2$. For example, $\Delta F^\circ_{CCl_4} - \Delta F^\circ_{He} = -6{,}200$ cal/mole of agent, using data of Figure 5 and $T = 37°C$. Since ΔF°_{He} must be at least $-RT$, $\Delta F^\circ_{CCl_4}$ must be at least $-6{,}820$ cal/mole. In the range from N_2O to CCl_4 (Fig. 1), log P plots linearly against $[R]$ and $\Delta(\Delta F^\circ)/\Delta\ [R]$ is about 103 cal/cm^3. With this relation between $\Delta[R]$ and $\Delta(\Delta F^\circ)$ and the assumption that binding of helium not related to its polarizability is negligible, ΔF°_{He} is about $RT + 103\ [R]$ or -670 cal/mole and $\Delta F^\circ_{CCl_4}$ is estimated at $-6{,}870$ cal/mole. It is evident from the correspondence of partial pressures in Figure 3 that about the same differences in energy apply both to interfacial sorption *in vitro* when the interface contains lipid and to anesthetic effect *in vivo*. Comparison with values for hydrate formation shows them to be somewhat smaller; for example

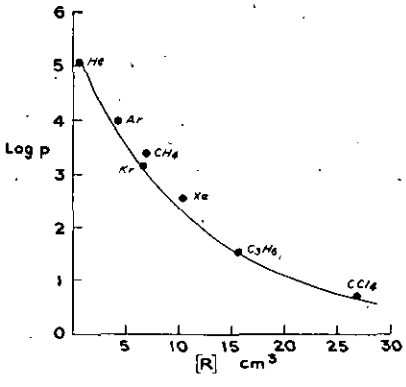

FIG. 5.—Isonarcotic partial pressures of symmetrical agents from Carpenter,[16] plus CCL_4 from Pauling.[1] Pressure in millimeters of mercury.

$$\Delta F^\circ_{Xe\text{-}5\ 1/4\ H_2O} \sim -10 \text{ kcal/mole}^1 \text{ and } \Delta F^\circ_{Xe\text{-mouse}} \sim -4 \text{ kcal/mole}$$

evaluated as above. Although our method of calculation is inexact, discrepancies of such magnitude are inconsistent with a simple hydrate theory of narcosis. Proponents of the hydrate theories[1, 2] have recognized this difficulty and suggested that the water in excitable structures is normally partially restricted and that the free energy of formation of narcotic-water complexes is correspondingly less. Proceed-

ing from this point of view, one could say that we have built and tested a crude membrane model in which such a phenomenon might be observed, and that thus far the binding energies agree satisfactorily with those calculated from *in vivo* experiments only when the model contains lipid. In so far as we understand the behavior of the model, it does not permit us to state whether the interactions occur primarily between lipid film and narcotic or between water and narcotic, facilitated by the presence of lipid. In either interpretation, our data suggest that lipid plays an essential role and show that even substances which are not intrinsically surface active can have profound effects when the composition of the interfacial phase is suitably chosen.[17] The sensitivity of the model to inert gases and the quantitative similarity of its reactions to their biological effect suggest that further studies of its changes of physical state under narcotics may be very informative.

We wish to thank Sheldon Gottlieb and other officials of the Linde Company of Tonawanda, New York, for helpful discussions and for their generosity in supplying purified rare gases for these studies.

* Supported in part by Grant H-6285 from the National Heart Institute.

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ABSTRACT

Cullen, S. C. and E. G. Gross

Anesthetic properties of xenon in animals and human beings with additional observations on krypton.

Science 113:380-382; 1951.

In a study of the possible narcotic effect of xenon, laboratory animals (mice, rats, rabbits) and human beings breathed either 50% xenon in oxygen or 50% nitrous oxide in oxygen, with CO_2 removed and oxygen added. It was found that: "...a chemically inert gas (by current standards) is capable of producing complete anesthesia, and, although it may not by virtue of its cost of manufacture prove to be a satisfactory agent commercially, it may materially assist in solving one of the important theoretical problems of anesthesia."

PHYSIOLOGICAL EFFECTS OF WORK IN COMPRESSED AIR.

G.C.C. DAMANT

NATURE, London 126: 606-608. 1930.

Physiological Effects of Work in Compressed Air.

THE average man always finds it surprising that our bodies can support such atmospheric pressures as 100 lb. per sq. in. without the slightest derangement of the delicate structures and processes on which life depends, but that, owing to a secondary effect, the return to normal pressure is accompanied by grave risk. A sojourner in compressed air inevitably soaks up a considerable volume of the nitrogen of the air into simple solution in the tissues and fluids of his body. So long as the pressure is maintained this gas remains hidden and harmless, but any reduction of pressure will drive it out of solution. The critical time in the management of compressed air workers is the period of decompression when they are passing from high air pressures down to the normal. Given time, the blood will carry off the excess gas and discharge it to the atmosphere in the lungs as the

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pressure falls, but a rapid decompression overloads the blood with excess gas, which bursts out in the form of bubbles and chokes the circulation with froth.

Compressed air is used by engineers to keep back water in sinking the foundations of bridges and in tunnelling under rivers; besides the men engaged in such work, divers using the ordinary rubber dress have to breathe air at high pressures. The joint discussion between the Sections of Engineering and Physiology of the British Association at Bristol attracted leading exponents of practice and theory in both these lines of work. Although divers are fewer in number than tunnel workers and their occupation is of less public importance, most of the recent research and experimental work has been directed to their special circumstances, and those responsible for diving work have been quick to take advantage of any new knowledge. An outstanding example is the action of the British Admiralty in being the first to adopt the entirely novel system for conducting the decompression which was devised by Prof. J. S. Haldane and has since been taken up by most of the navies of the world. Its value for divers has now been established by twenty-five years' experience, and particularly in some recent salvage operations where more than five thousand dives were made at pressures between 50 lb. and 60 lb. per sq. in. without accident.

The circumstances of tunnel workers differ from those of divers in that they have to work much longer shifts under pressure, though the pressures themselves are never so high as those experienced by divers. In times past the mortality among the tunnel and caisson workers from compressed air illness was so heavy that many countries adopted State regulations designed to protect the men by limiting the length of shift and enforcing some sort of gradual decompression. Undoubtedly these regulations have done good, but in the light of modern knowledge and experience they could be improved so as to give greater security to the men while avoiding the costly waste of working time resulting from some of their clauses.

If the civil engineering of the future is going to call for higher pressures than the 40 lb. or 45 lb. per sq. in. that has been the limit hitherto, it is certain that these rules will be found badly wanting, and Sir Ernest Moir in opening the discussion indicated that the time has come for concentrating the available knowledge and experience in producing a rational and practicable code or system for the use of engineers charged with the control and safety of workers in such air pressures. One of the difficulties of the matter is that there is a very great difference in the susceptibility to compressed air illness of different individuals, which at present can only be discovered by trial, so that cases of illness are still to be expected under a system which is quite safe for the average man. Fortunately, a cure is available in 'recompression', which if applied sensibly and at once is certain. Sir Ernest Moir, by his introduction and employment of the 'medical air lock' for applying this treatment, has been the means of saving many hundreds of lives.

Dr. M'Master, who described the latest British experience at the Silent Valley dam of the Belfast waterworks, mentioned many points which seemed to show that secondary factors, such as the temperature and humidity of the workings or a slight vitiation of the air supply, which would be unimportant in diving work, made a marked difference in the number of cases. In the sea we have a continuously graded range of hydrostatic pressures through which the diver can be decompressed as he gradually ascends, but in caisson work the pressures can only be roughly adjusted to the theoretical requirements, so that, though all serious illness was prevented, a good many minor but painful cases of 'bends' had to be treated by recompression, and to cure them it was found necessary to recompress many of the patients to 5 lb. above the pressure at which they had been working (about 35 lb.). This contrasts strangely with experience of divers working at 50 lb. pressure, who when they develop similar symptoms are nearly always cured by recompression to a mere 15 lb. or so, which greatly simplifies and shortens the treatment. But divers, being on board ship, are generally treated immediately the symptoms appear, while men on engineering work may have time to get home before they become ill and then may not present themselves for treatment for some hours. This probably underlies the difference, and the point illustrates one of the difficulties of the engineer; he cannot very well insist on a shift of a hundred men hanging about round the works for an hour or two after they have finished work for the day on the off chance that one of them may develop compressed air illness, but the salvage officer with his handful of divers can easily arrange for there to be no means of getting ashore until the danger period is past.

Mr. Davis, jun., in the course of an interesting review of the history of the subject, described apparatus lately introduced by Messrs. Siebe, Gorman and Co. for very deep diving, including a large steel pressure chamber which is lowered under water so that the diver can enter it on the completion of his job and be hoisted inboard without releasing the air pressure from his body. A long decompression can then be conducted in warmth and dryness instead of under water with much discomfort and fatigue as hitherto, while the ship is free to slip her moorings and get clear or fire blasting charges, which could not otherwise be done until the diver's decompression was finished.

Sir Leonard Hill and Commander Selby spoke of the experimental diving which has been carried out for the Admiralty to more than 300 ft. or 130 lb. pressure, using the Davis decompression chamber and other special devices. One unexpected and rather awkward finding was that, though all the divers were picked men who had been put through a specially searching medical examination, some of them became abnormal mentally (or emotionally as Sir Leonard Hill put it) whilst under this high pressure, and on their return to the surface could remember nothing of what they had been doing before they began to ascend. This effect

might be attributed to the high partial pressure of oxygen in pure air when breathed at 130 lb., or to impurities in the air which was actually supplied to the divers, but Sir Leonard Hill has made tests on the same men which satisfy him that neither oxygen nor carbon dioxide is responsible. It seems to be an extreme case of the subtle change in character and behaviour which comes over some men at less high air pressures and is well known to experienced diving officers. Divers affected in this way generally keep fairly quiet on the subject, as they do not wish to be thought excitable or foolish about their work. The steel decompression chamber was employed to great advantage in these experimental dives, but, as Prof. Haldane pointed out in concluding the discussion, the stages of decompression given to the men were not calculated on the principles which have proved so satisfactory hitherto and do not appear to have given sufficient margin of safety. This is a matter which can easily be rectified if necessary without invalidating the ingenious methods and appliances which have been elaborated for this extremely difficult sort of diving.

The Italian divers now working on the wreck of the *Egypt* at a depth of 400 feet have cut out all danger of compressed air illness and the need for a host of hampering precautions by using the Neufeldt and Kuhnke armoured apparatus, which, though flexibly jointed, sustains the enormous hydrostatic pressure of 170 lb. per sq. in. corresponding to that depth and enables the man inside to breathe air at atmospheric pressure. The gain in safety and economy of working time which results is partly offset by a loss of mobility and manual efficiency as compared with a rubber-dressed diver, but this again is compensated by the elaborate grabs and machinery of the salvage ship. The diver on the bottom has become less the working agent and more the eye and brain directing engines which are lowered to him and worked from above. Conceivably some such semi-automatic system of working may develop in caisson and tunnel work, though it does not seem called for with the pressures likely to be used in the near future. None of the speakers expressed any doubt that all serious illness could be prevented by suitable decompression: the real problem is to key these lengthy decompression periods in with the design of the tunnel, the scheme of work, and the system of shifts, so that they may become something less wasteful and unsatisfactory than hours of enforced idleness passed in dismal steel cylinders.

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J. Ind. Hyg. & Toxicol. 20:511-520. 1938.

THE USE OF NEW EQUIPMENT AND HELIUM GAS IN A WORLD RECORD DIVE*

EDGAR END

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THE history of diving is a record of man's slow progress in extending his working realm into the depths of the seas which cover more than two-thirds of the earth's surface. Augustus Siebe invented the first practical diving suit in 1819, and his improved model, as introduced in 1837, is in almost universal use today. This suit consists of an incompressible metal helmet and breastplate which fit over the diver's head and shoulders and a flexible, waterproof dress which covers all the rest of his body with the exception of his hands. The diver's hands usually protrude uncovered through elastic cuffs but may be protected by waterproof gloves or mittens. Manually-operated air pumps, motor-driven compressors, or cylinders of compressed air at the surface supply the diver with air through a flexible hose.

A diver wearing this type of equipment requires that at least 1½ cubic feet of air per minute must pass through the helmet of the diving suit in order to prevent the accumulation of carbon dioxide in excessive amounts (1). In addition to providing ventilation, this air which enters the diving suit under pressure partially distends the upper portion of the dress to permit easy respiratory movements and equalizes increasing water pressure when the diver descends. For each 2 feet that a diver descends, there is an added water pressure of almost a pound on every square inch of his 2000 or more square inches of body surface. Thus a descent of a little more than 2 feet increases the total pressure on his body by about a ton. Unless this pressure is equalized by an increased amount of air entering the diving suit from the surface, the air inside of the suit will be compressed according to Boyle's law and will be forced from the compressible dress into the incompressible helmet, and the diver's body will be forced into the helmet with it. This accident is known as a "squeeze" and is particularly dangerous when there is a sudden, relatively great increase in external (water) pressure over air pressure in the suit, such as occurs when a diver falls through a considerable distance under water or when the pressure inside the diving suit drops suddenly, owing, for example, to escape of air through a torn air hose from a helmet not equipped with a functioning safety valve. In speaking of a "squeeze," the United States Navy Department Diving Manual states: "Extreme cases have been known where the diver has been molded into his helmet so that it was practically impossible to remove it."

* Received for publication May 25, 1938.

Unfortunately the hose on which a diver relies for his air supply is a constant menace to him when he is working in or near wreckage, for it easily becomes entangled and traps him on the bottom. While it is possible for a diver to cut his life line and telephone cable if necessary to free himself, he cannot cut his air hose without beginning immediate ascent; and even if he should reach the surface before the small supply of air in his helmet is exhausted, such rapid ascent will usually subject him to the dangers of compressed air illness. During salvage operations on the sunken submarine "F-4," almost 20 per cent of the dives reported by French (2) resulted in divers becoming fouled on the wreck, and when we consider the nature of the work that these men perform and the obvious shortcomings of the equipment provided for their use, it is not surprising that the history of underwater salvage is well supplied with stories of daring rescues of entrapped divers by their comrades.

Compressed Air Illness

Compressed air illness, which is probably the greatest danger that a diver faces, is a condition encountered whenever men breathe air under a pressure of more than 15 to 19 pounds per square inch for a considerable period of time and are then quickly brought back to atmospheric pressure. Since the monumental work of Paul Bert (3), it has been generally accepted that this condition is caused by the presence of nitrogen bubbles in the blood and body fluids. This inert gas, which makes up about four-fifths of the air that we breath, enters the body through the lungs and dissolves in increased amount according to Henry's law when air is breathed under pressure. After a sufficient quantity of this gas has entered the body, a sudden reduction in the pressure to which the individual has been subjected will permit the nitrogen to come out of solution in the form of bubbles. In the blood vessels these bubbles act as gas emboli; and if they appear extravascularly they may cause dehiscence of delicate tissues.

The formation of nitrogen bubbles during decompression can usually be prevented by lowering the pressure slowly in order to allow the nitrogen to escape from the body through the lungs. This practice is the basis for the decompression tables proposed by Boycott, Damant, and Haldane in 1908 (4) which are in general use today. Unfortunately, decompression according to standard tables will not always prevent compressed air illness (1, 5), and the length of time necessary for decompression is a considerable factor in limiting productive diving to relatively shallow water or to deep dives of very short duration. According to standard United States Navy decompression tables, a diver who descends to a depth of 250 feet and remains there for 20 minutes must spend 2 hours and 26 minutes in decompressing. Should he extend his stay on the bottom 10 minutes longer, his decompression time will increase by more than an hour.

An explanation of compressed air illness based entirely upon theories of bubble formation is not altogether satisfactory (6). In this connection, a significant observation already mentioned in a paper by Swindle (7) has been the constant finding of a marked

state of agglutination of erythrocytes in experimental animals subjected to compressed air illness in this laboratory. A discussion of the probable significance of this observation will be attempted in a later paper, but it can be stated at this time that agglutination of erythrocytes appears to be the primary disturbance in compressed air illness and that bubble formation may be looked upon as a serious complicating factor. Of practical significance in this connection is the observation that alkalinization apparently influences this condition favorably, which has led us to employ the ingestion of sodium bicarbonate as a prophylactic against compressed air illness during experimental deep dives.

Mental Changes

Despite the dangers which divers face, they have penetrated deeper and deeper into the depths of the sea and in so doing have uncovered a new and dangerous phenomenon which has for a time limited practical diving to a maximum depth of 300 feet. This condition consists of an alteration in the diver's mental state, of which Phillips (8) says: "During the 1930 season, when working, or in many cases resting, at from 270 to 300 feet, the diver experienced what to him were new sensations; he found that it was much more difficult to exercise the quick decision essential for successful diving." That these mental changes may incapacitate a diver for careful work and render him dangerous to himself is well illustrated in the case of one man who became so disturbed at a depth of 270 feet that he attempted to unscrew the faceplate from his helmet in order to escape from the diving suit. Attempts have been made to explain this alteration in a diver's mental state on the basis of the high partial pressure of oxygen in the air that he breathes, but this theory has been largely disproved (9). Others have attributed it to the fact that nitrogen, in its greater affinity for fats than for water, resembles certain of the aliphatic narcotics according to the Meyer-Overton law and hence may act as a depressant when breathed under pressure (10). Others, among them some unusually successful divers who have been questioned on this subject (8, 11, 12), feel that such abnormal conduct on the part of a diver in deep water is a manifestation of claustrophobia. Whatever its true cause may be, this condition may eventually become a deciding factor in determining the maximum depth to which a human being can descend in a flexible diving suit.

New Diving Suit

During the past few years there has been developed by Mr. Max E. Nohl of Milwaukee, Wisconsin, a new type of diving suit designed for the purpose of making diving safer and more practical. The physiological problems which have arisen during construction and testing of this equipment have been investigated in this laboratory. A discussion of this new diving suit, which appears to have fulfilled its inventor's expectations in every respect and which recently permitted him to establish a new world record for deep diving, will be attempted in this paper.

The new diving suit is self-contained, the diver carrying his air supply under pressure in steel cylinders

on his back. Since he is no longer dependent upon the surface for his air supply and has no trailing air hose to become entangled, he can enter wreckage from which an ordinarily-clad diver would be barred. Moreover, the expensive pumps, compressors, or banks of compressed air cylinders formerly seen on diving boats are no longer needed. Wearing three steel cylinders which take the place of the back weights worn on standard diving suits, the diver has an air supply sufficient for more than 15 hours' submersion. In one of the steel cylinders is carried a respirable gas mixture which the diver admits into the suit to equalize increasing water pressure as he descends. The other cylinders contain oxygen which enters the suit at a rate carefully controlled by the diver to satisfy his metabolic requirements. A mask which he wears over his mouth and nose is equipped with valves which direct all exhaled air through soda lime to remove carbon dioxide; and a microphone is so placed in the mask that not only the diver's conversation but also his respirations are audible to those at the surface through a telephone circuit.

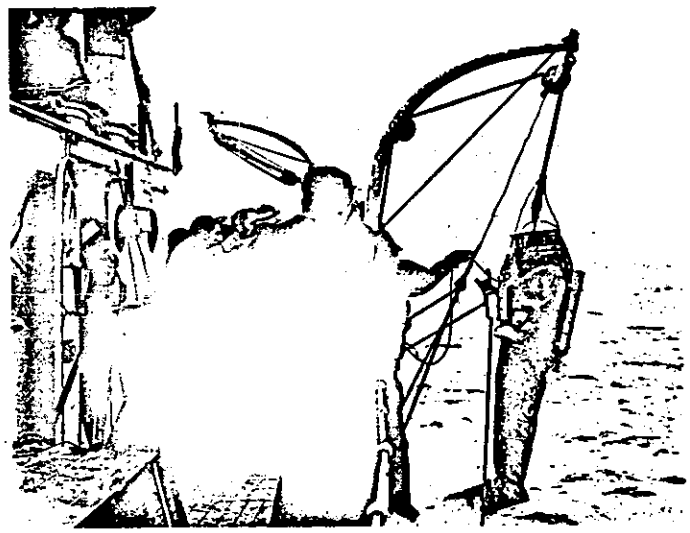

FIG. 1. The diver is shown suspended by his life line from a davit. His left hand rests on his belt with his left wrist touching the valve which controls admission of distention gas into the diving suit. His right hand rests on a braking lever which permits him to stop at will on his descending line during ascent or descent. The cylindrical window of the diving helmet, which allows 360° vision, is plainly visible, as are the cylinders on his back. It should be noted that the diver's entire weight is supported by cables and chains which originate in the ring at the top of his helmet and finally pass between his legs to form a sling for his body when he is suspended out of water.

This suit differs from other self-contained diving suits in employing a separate distention mixture and oxygen supply. The Fleuss-Davis self-contained suit, for example, uses a mixture of oxygen and compressed air in equal parts to serve both purposes,

but the need of replacing this mixture in the suit when it becomes vitiated prohibits a diver from carrying enough oxygen-enriched air for prolonged submersion. Even if it were possible for him to dive very deep in such a suit, the diver would be endangered by breathing a mixture so rich in oxygen for any length of time under great pressure. In Mr. Nohl's suit, by reducing or temporarily interrupting the flow of oxygen as he descends and by increasing the flow as he ascends, and by using distention mixtures in which the oxygen percentage as determined beforehand is reduced in accordance with the planned depth of the dive, the diver can provide himself with a breathing mixture in which the partial pressure of oxygen closely approximates that met with in atmospheric air. This is a condition which Sayers, Yant and Hildebrand (13) regard as being very desirable but which has never been attainable with ordinary diving equipment and which is directly opposed to conditions prevailing in the Fleuss-Davis type of suit.

FIG. 2. The diver, without face mask and rebreathing apparatus, illustrates the method of donning helmet and pressure cylinders. The elastic latex neck of the dress is pulled up over the lower portion of the helmet and held tightly in place by two metal drawstraps, forming a watertight union and materially shortening the time necessary for dressing the diver.

The wearer of the new self-contained diving suit uses a life line and a telephone cable, but should it become nec-

essary for him to do so, he can sever these and rise to the surface at a controlled rate, stopping for decompression during ascent. In order to do this, he first learns his decompression schedule from the surface and can then cut telephone cable and life line to free himself from whatever is fouling him. A light but strong manilla line is carried in a pocket on the diving suit, and when the diver has worked his way into the open, he attaches one end of this line to any fixed object on the ocean floor or to his heavy lead-soled shoes, which are then released from his feet and serve as an anchor. Slight overinflation of the suit or the act of releasing his shoes will make the diver positively buoyant, and he will begin to rise, governing his rate of ascent by means of the manilla line, which is used as a brake, and by allowing expanding gas to escape from the suit through an exhaust valve on the helmet. Markers on the line indicate the distance through which he has ascended, and stops can be made at appropriate depths for decompression. A luminous-dial watch on the instrument panel of the helmet permits these stops to be of the proper duration; and when the diver reaches the surface, the bright metal portions of his helmet and the light color of his dress make detection easy.

Because of the possibility of using any respirable gas mixture for distending the new diving suit, it has become possible for the first time economically to employ the helium-oxygen mixtures suggested for divers by Hildebrand (14) and tested on small animals by Sayers, Yant and Hildebrand (13) more than a decade ago. These investigators showed that the use of helium-oxygen mixtures as a substitute for compressed air permits decompression of small animals in from one-fourth to one-third of the usual time. In our own experiments on human subjects decompression in as little as one-twenty-third of the usual time has been accomplished by breathing helium-oxygen mixtures under pressure (15). While these results were obtained under experimental conditions and are not directly applicable to actual diving, they are encouraging indications of the substantial reductions in decompression time that eventually may be achieved by this means.

Helium, which like nitrogen, is odorless, tasteless and colorless, is a superior type of inert diluent for the oxygen supplied to a diver because it is only about half as soluble as nitrogen and about three times as diffusible. Thus it is felt that a diver breathing helium and oxygen under pressure for an indefinite period of time will become saturated with only half as much inert gas as he would if he were breathing compressed air, and during decompression the helium will escape from his body about three times as rapidly as nitrogen would. In addition, there appears to be a marked absence of psychological change in individuals breathing helium-oxygen mixtures under pressure (15). Unfortunately, up to this time the use of helium-oxygen mixtures in actual diving has never been adopted because of the difficulty of recovering and purifying such mixtures after they have been used to ventilate the helmet of the ordinary diving suit, despite the fact that any material advance in deep diving must be looked for along these

lines. As Behnke, Thomson and Motley stated in 1935 (10): "An artificial gas mixture for divers is essential if operations at great depths (above 300 feet) are carried out, and for caisson workers if the exposure at and higher than 4 atmospheres be continued over long periods of time."

In the new diving suit a small amount of helium is sufficient for a dive since this gas is constantly rebreathed and does not escape from the suit until the diver begins ascent. Furthermore, more complex mixtures such as helium, oxygen, and nitrogen can be used in order to keep low the solution pressure of each individual gas in the blood and thus reduce the danger of their forming bubbles during decompression. This method was employed in our early experiments in which helium was used to displace successively greater percentages of nitrogen in prepared mixtures breathed under pressure (15).

Another advantage of the new diving equipment is the possibility of hastening decompression by flooding the suit with pure oxygen when the diver is hanging suspended at depths of 60 feet or less during decompression. The use of oxygen for this purpose is based on the fact that when the alveoli of the lungs are filled with a mixture rich in oxygen and consequently low in inert gas, the inert gas which is under high solution pressure in the blood tends to pass rapidly out into the alveoli and to escape from the body (16, 6). Heretofore, without the use of accessory equipment, recompression chambers, or the Davis Submersible Decompression Chamber, it has been impossible to employ this principle in decompressing divers. Now, however, a diver wearing the new self-contained diving suit merely opens the exhaust valve widely each time that he is raised to a new decompression stage and allows as much gas as possible to escape from the suit, which he then refills with pure oxygen from the cylinders on his back. In addition, a fitting on the diving suit permits the instantaneous attachment of a standard air hose through which oxygen can be supplied from the surface or down which compressed air can be blown to ventilate the helmet and hasten decompression after dives in which helium-oxygen mixtures have been breathed.

Record Dive

After carefully testing his equipment in a series of successively deeper dives during the autumn of 1937, Mr. Nohl decided to attempt to establish a new world record for deep diving. Great Britain claimed the old record with a dive of 344 feet (5, 8), while the United States Navy record is still apparently 306 feet, the depth to which Frank Crilley descended in 1915.

Through the interest of the United States Coast Guard, the patrol boat "Antietam" was placed at our disposal, and Mr. Nohl's record dive was made from its decks on December 1, 1937, at a point in Lake Michigan about 12 miles off Port Washington, Wisconsin. The vessel was anchored in 70 fathoms (420 feet) of water, as determined by soundings made with lead and gauge by Commanding Officer E. C. Whitfield. Additional measurements on the diver's descending line and telephone cable during the dive confirmed these soundings.

During the entire dive, Mr. Nohl was in communication with the surface by telephone. He was swung over the side of the "Antietam" from a lifeboat davit, as can be seen in figure 1, and entered the water at 12:50 P.M. He descended to the 200 foot level in 3 minutes and requested to be held there until his ears became adjusted to the pressure. During the pause which followed, a member of the surface crew carelessly allowed the phone cable to run out of its own weight, forming a loop through which Mr. Nohl passed when he again descended. This drew him tightly against his descending line and caused a delay of 26 minutes during which time he worked his way down to the 240 foot level.

When it became evident that he would be unable to free himself without cutting his telephone cable, Mr. Nohl was raised rapidly to the surface, disentangled, and again allowed to descend, reaching the bottom 9 minutes after entering the water for the second time. He spent 9 minutes searching the lake bed in a small circle and conversing with those on the surface by telephone. Following this, he was raised at a rather slow rate, reaching the 200 foot level in 12 minutes and the 30 foot level 10 minutes later. He remained at the 30 foot level for 22 minutes, at the 20 foot level for 28 minutes, and at the 10 foot level for 46 minutes. Thus 118 minutes were spent in raising the diver to the surface. Although no attempt was made to reduce the decompression time greatly after this very deep dive, the total decompression was almost 30 minutes less than would have been required for the first portion of the dive (up to the time that the diver was pulled to the surface and disentangled) had he been breathing compressed air instead of a mixture of 80 per cent helium and 20 per cent oxygen. The extemporaneous decompression schedule employed, which undoubtedly provides a substantial margin of safety, proved entirely satisfactory in preventing the development of any indications of compressed air illness. At the 30 foot stage and at each succeeding stage Mr. Nohl allowed as much gas as possible to escape from the diving suit, which he then refilled with pure oxygen from the cylinders on his back.

Our record of the dive is as follows:

Date: December 1, 1937.
Diver: Max Nohl.
Place: Lake Michigan, 43° 21′ N., 87° 37′ W.
Depth of water: 420 feet.
Purpose of dive: Experimental.
Breathing mixture: 80% helium—20% oxygen.
Time:

12:50	P.M.	Entered water.
:51	"	At 100 feet.
:52	"	At 165 feet.
:53	"	At 200 feet.
1:19	"	Began ascent from 240 feet (fouled).
:23	"	Reached surface.
:25	"	Cleared; re-entered water.
:34	"	On bottom (420 feet).
:43	"	Began ascent.
:55	"	At 200 feet.
2:05	"	At 30 feet.
:27	"	At 20 feet.
:55	"	At 10 feet.
3:41	"	At surface.

At no time during the dive was there any indication of an alteration in the diver's mental state due to pressure, and it is tempting to attribute this to the fact that a helium-oxygen mixture was breathed instead of compressed air. However, there are insufficient

data on this subject to justify such a sweeping conclusion at this time, and it must not be forgotten that Mr. Nohl's calm temperament and unusual intelligence may be very important factors in determining his reaction to pressure, as Shilling and Willgrube have pointed out (17). Although at a depth of 420 feet Mr. Nohl was under a pressure of 182 pounds to the square inch, or more than half a million pounds of pressure on his entire body surface, it seems probable that he might have descended much deeper on this occasion had the depth of the lake at that point permitted him to do so. Because of the difference in the weight of sea water and fresh water, Mr. Nohl's dive is equivalent to a dive of a little more than 410 feet in the ocean.

On this, as on all previous occasions, the self-contained diving suit functioned perfectly from a mechanical standpoint. Throughout the dive Mr. Nohl's respirations were slow and regular, and although the temperature of the water was close to the freezing point, he was protected by a fleece-lined underdress and by waterproof mittens and did not suffer from the cold. There was no leakage of water into the diving suit, in marked contrast to conditions usually encountered in standard diving suits, which are seldom waterproof in the true sense of the word. It is to be remarked that the method of attaching the strong latex-dipped dress of the new suit to the helmet by means of two metal draw-straps permits a perfectly tight union and great ease in dressing the diver. Mr. Nohl's condition after his 420 foot dive was apparently superior to Frank Crilley's condition after his 306 foot Navy record dive, for although Crilley's record was made in Pearl Harbor, Honolulu, with the surface temperature of the water at 70°F., the Navy report states (2): "The diver was wet and cold but otherwise showed no ill effects from his dive."

We wish to express our sincere appreciation to the United States Coast Guard and particularly to Lieutenant E. C. Whitfield and Boatswain John Hark of the "Antietam" for their great help in establishing this diving record and to Mr. James T. Howington, vice president of the Girdler Corporation, who has generously supplied us with all of the helium used in our work.

Summary

The problems met with in diving are reviewed in their relationship to the development of a new self-contained diving suit which was recently worn in a world record dive. This new equipment renders a diver independent of the surface for his air supply; it permits him to work in wreckage from which a trailing air hose would bar him, allows independent ascent to the surface with timed stops for decompression, enables him to adjust the partial pressure of oxygen in his breathing mixture so that it approximates that met with in atmospheric air, permits the economical use of artificial gas mixtures such as helium and oxygen, and provides for inhalation of oxygen to hasten decompression. Wearing this suit and breathing a mixture of 80 per cent helium and 20 per cent oxygen to permit easy comparison to compressed air, the inventor of this equipment recently descended 420 feet in

Lake Michigan to establish a new record for deep diving. Although at that depth he was under a pressure of more than 182 pounds to the square inch or a total of more than half a million pounds on his entire body surface, it appears certain that he could have descended deeper had the depth of the lake at that point permitted. At no time were there noted any mental changes such as have been described in men breathing compressed air under great pressure, and it is speculated that this freedom from mental change may have been due to the nature of the helium-oxygen mixture employed. A detailed description of the record dive and the decompression schedule employed is given.

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Proceedings

SECOND SYMPOSIUM on UNDERWATER PHYSIOLOGY

February 25-26, 1963
Washington, D. C.

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Editors

Prepared for the
Office of Naval Research
Washington, D. C.

by the
Mine Advisory Committee
National Academy of Sciences—National Research Council

Publication 1181
National Academy of Sciences—National Research Council
Washington, D. C.
1963

III-12-97

MEASUREMENT OF INERT GAS NARCOSIS IN MAN

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Numerous investigations have shown that air at raised barometric pressures exerts certain mental and phychomotor effects on man, such as euphoria, confusion, slowed mental activity, motor incoordination, and impairment in performance. Behnke, Thomson and Motley[1] who were the first to attribute these effects to the high partial pressure of nitrogen, contended that subjective intoxication may occur at pressures as low as 3.0 atm abs (atm). This corresponds to a diving depth of about 60 feet. Kiessling and Maag[2] have recently reported that changes in objective performance are demonstrable at 4.0 atm. Case and Haldane[3] also ascribing the narcotic action to nitrogen excess, found, on the other hand, that at pressures as high as 8.6 atm there was only a slight intoxication with no reduction in manual dexterity. They also made the important observation that minimal amounts of carbon dioxide in the inspired air greatly increased the deterioration in performance at raised pressure. Damant[4] attributed part of the intoxicating effects to the increased oxygen pressure.

Bean[5] and Buhlmann[6] have expressed doubt that nitrogen is responsible for compressed air narcosis, and have contended that the sole causative factor is a rise in body CO_2 tension. Increased breathing resistance due to raised gas density at pressure would result, according to Buhlmann, in hypoventilation and impaired CO_2 elimination. Bean reasoned that raised gas density would lead to increased difficulty in CO_2 diffusion and mixing in the alveoli and in this way to reduced CO_2 output.

Finally, it has also been suggested that the subjective symptoms experienced in work at high atmospheric pressure are manifestations of anxiety[7] and claustrophobia, or are caused either by a combination of all of the aforementioned factors or else by the pressure itself[9].

However, as evidenced from recent encephalographic studies of Bennett and Glass[10] there seems to be no doubt that high nitrogen pressure constitutes an important causative factor of compressed air narcosis. At atmospheric pressure the solving of arithmetical problems blocked the occipital alpha rhythm in subjects of the "responsive" or R type. No such blocking occurred after a variable time at increased air pressure, indicating that a fundamental change occurs in the central nervous system when a certain tension of nitrogen is reached. If nitrogen in the inspired air was replaced by helium, no abolition of blocking took place.

The divergent opinions as to the mechanism of compressed air narcosis may to some extent be explained by the fact that, at raised barometric pressures, there are simultaneous increases in alveolar oxygen pressure, alveolar nitrogen pressure, and gas density. Experimental situations in which the subjects are exposed merely to "normal" air at different barometric pressures will therefore

not permit any differentiation between these factors as to their possible narcotic effects.

In collaboration with Drs. M. Frankenhaeuser and V. Graff-Lonnevig we have made an attempt to separate the possible factors responsible for compressed air narcosis by studying the changes in human performance induced through exposure to different nitrogen-oxygen gas mixtures at increased ambient pressures*. For this purpose 12 young subjects were tested individually on three psychomotor tasks while breathing different gas mixtures at normal and at raised pressures in a dry compression chamber. To exclude admixture or expired carbon dioxide, all gas mixtures were inhaled from Douglas bags via a low resistance and small dead space (about 10 ml) breathing valve. The conditions were as follows:

TABLE I

Condition	Ambient pressure (atm abs)	Inspired gas mixture	Partial pressures of inspired gases (atm abs)	
			Oxygen	Nitrogen
A	1.0	Air	0.20	0.74
B	1.0	100% O_2	0.94	—
C	4.2	5.2% O_2 in N_2	0.22	3.92
D	5.0	Air	1.03	3.91
E	6.6	39.8% O_2 in N_2	2.60	3.94

Tests for simple and four-choice visual reaction times and mirror drawing were used. The task on mirror drawing was to move a stylus as fast as possible along a track, cut out in a metal plate so as to form a five-pointed star, and visible only in a mirror. The track was provided with saw-tooth notches which tended to catch the stylus. The time score was the time spent to complete one run, and the error score the total time of contact between the stylus and the metal contours of the track. The five conditions and the tasks within each condition were rotated at random order. At least four to five minutes were allowed to pass after any change in ambient pressure or of inhaled gas mixture before a test series was started.

The results obtained in the five conditions are presented in Table II. A rise in air pressure from 1.0 to 5.0 atm caused only a slight tendency toward impaired performance (a two to three per cent increase in simple and choice reaction times). These observations agree with those of Case and Haldane[3] but

*A full account of the present work will be published in Acta physiol. Scand.

TABLE II

Time and Error Scores in Psychomotor Tasks
(mean values for 12 subjects)

Task	Condition A Air, 1.0 atm	B O_2, 1.0 atm	C 5.2% O_2 in N_2, 4.2 atm	D Air, 5.0 atm	E 39.8% O_2 in N_2, 6.6 atm
Simple reaction, sec	0.243	0.242	0.241	0.248	0.256
Choice reaction, sec	0.671	0.683	0.685	0.691	0.698
Mirror drawing, time, sec	9.16	9.25	9.47	9.24	8.93
Mirror drawing, error sec	2.89	2.85	3.39	3.11	3.34

are at variance with those of Shilling and Willgrube[9] and Kiessling and Maag[2], who at approximately the same pressures observed a significant 10 and 21 per cent increment in simple and two-choice visual reaction times, respectively. These quantitative deviations in results may possibly be due to pronounced individual differences in susceptibility to air narcosis or to differences in the general experimental procedure. Since the addition of even minimal amounts of carbon dioxide to the inspired air may greatly enhance the narcotic action of air at pressure[3], the effects observed in deep-sea divers and in subjects breathing air in a compression chamber might in part be due to the carbon dioxide that accumulates in the diver's helmet or in the chamber.

That pure air at 5.0 atm pressure produced only slight changes in objective performance in resting subjects is not inconsistent with the observations of Behnke et al[1] that subjective intoxication may occur at pressures as low as 3.0 atm. In experiments dealing with the effects of nitrous oxide and other drugs on various mental functions, Frankenhaeuser et al[11,12,13] found that performance may remain relatively undisturbed even when subjective changes are pronounced.

If oxygen was added to the inspired air (39.8% O_2 in N_2 at 6.6 atm), the impairment in performance became more marked, indicating a synergistic rather than antagonistic action of nitrogen excess and oxygen excess. From this it may be concluded that compressed air narcosis is not due to interference with oxidation in the tissues by nitrogen under high pressure.

By comparing the data obtained at pressure (Conditions C, D and E), the effects of increasing the oxygen pressure at a constant nitrogen pressure of 3.9 atm were determined. As shown in Figure 1, the changes in performance increased with increasing oxygen pressure, and reached a statistically significant level ($P < 0.05$) in two of the tasks when the rise in oxygen pressure amounted to

2.4 atm. This observation supports the view that oxygen excess has a potentiating effect on compressed air narcosis.

In a previous investigation we found that increasing the oxygen pressure to 3.0 atm at a low nitrogen pressure had but very slight effects on performance[14]. The effects of oxygen thus seem to be more marked under conditions of high nitrogen pressure. Our present data do not allow any definite conclusion as to the immediate cause of the observed differences in oxygen effects.

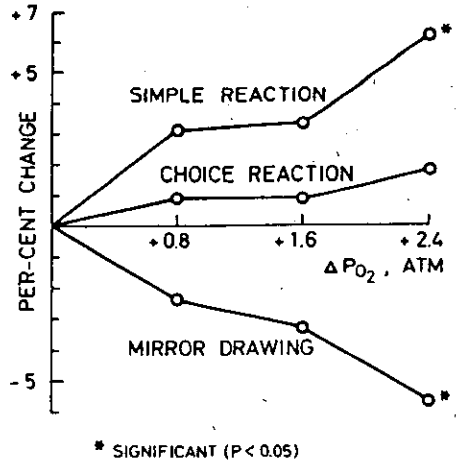

Figure 1. Changes in Performance Induced by Increasing the Oxygen Pressure at a Constant High Nitrogen Pressure (3.9 atm) (mean values for 12 subjects)

It seems possible, however, that oxygen excess may act indirectly by interfering with carbon dioxide elimination from the tissues. This conclusion is based on the following reasoning. Lambertsen and co-workers[15,16,17] found that the inhalation of oxygen at 3.0 -3.5 atm caused an increased activity of the respiratory center due to local accumulation of carbon dioxide, a 5-6 mm Hg fall in alveolar and arterial Pco_2, and a 3 mm Hg increment in internal jugular Pco_2. This indicated that the CO_2 tension in the respiratory center also increased by about 3 mm Hg. To induce a similar rise in internal jugular Pco_2 by carbon dioxide breathing at normal atmospheric pressure, the inspired CO_2 tension would have to be increased to about 20 mm Hg. However, a similar rise in the inspired CO_2 tension causes a marked impairment of performance at 10 atm but no deterioration in manual or arithmetical skill at normal atmospheric pressure[3].

From these observations it may be inferred that 1) an increase in inspired Po_2 to higher than normal levels causes a rise in tissue Pco_2, 2) high N_2 and CO_2 tissue tensions have a synergistic narcotic action and 3) an isolated, moderate increase in tissue Pco_2 has no demonstrable narcotic effect. These three statements would seem to be compatible with our findings that, at a high Pn_2 level, the performance changes increased with increased inspired Po_2, whereas at a low Pn_2 level a similar increase in inspired Po_2 had no significant effect on performance.

By comparing condition C with A, and D with B, the effects of raising the nitrogen pressure alone were revealed. From the results of these comparisons it may be concluded that, at rest, nitrogen pressures up to 3.9 atm have but very slight effects on objective performance. Similarly, in a previous investigation on breath-holding at elevated pressures, we have obtained evidence that nitrogen pressures below 4.0 atm have little if any narcotic effect on the respiratory center[18].

The view that compressed air narcosis is caused solely by a rise in the alveolar and tissue CO_2 tension due to hypoventilation or increased difficulty in CO_2 diffusion in the lungs may hold for rapid compression. For "steady state" conditions, however, this hypothesis is contradicted by recent observations on the CO_2 output and alveolar Pco_2 in man at elevated pressure.

In resting subjects after 15 min air breathing at 3.5 atm, Lambertsen et al[17] found no reduction in CO_2 output and a slight fall in alveolar Pco_2, implying alveolar hyperventilation rather than hypoventilation. The last-mentioned observation was confirmed by Hesser and Holmgren[19], who also reported that when the nitrogen pressure alone was increased to 3.8 atm, the alveolar ventilation decreased somewhat. Evidence was presented that this suppression of ventilation was caused by the increase in gas density and breathing resistance rather than by any depressant action of high nitrogen pressure on the respiratory center. It was also concluded that the increase in alveolar ventilation observed during air breathing at 4.0 atm was due to the respiratory stimulating effect of high Po_2 being greater than the suppressing effect on ventilation of increased breathing resistance.

At present it cannot be ascertained whether the same relationship between these two opposing effects on respiration prevails at air pressures higher than 4.0 atm and/or during muscular exercise. It seems possible that, in moderate and heavy exercise at elevated pressure, the increment in respiratory minute volume would result in a marked rise in breathing resistance and, hence, in a suppression of ventilation and a consequent rise in body CO_2 tension. If one assumes a synergistic narcotic action of N_2 excess and CO_2 excess, this mechanism, together with an increase in inspired Pco_2 due to accumulation of CO_2 in the helmet, might well explain the marked symptoms of compressed air intoxication that divers usually experience at great depths.

Investigations currently being performed by Adolfson in our laboratory support the hypothesis that muscular exercise might enhance the impairment of performance observed at raised air pressure. This is apparent from Figure 2, which shows that, with increasing ambient pressure, the loss in manual dexterity was much greater during exercise than at rest.

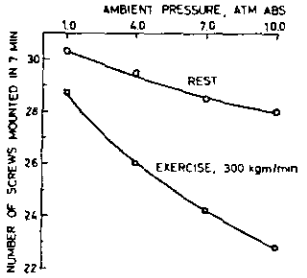

Figure 2. Effects of Raised Barometric Pressures on Manual Dexterity (screw-test at Rest and during Exercise (bicycle) (mean values for 10 subjects)

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VOLUME XVIII. JULY, 1932. No. 3.

Journal of the Royal Naval Medical Service.

Original Articles.

DEEP-SEA DIVING.[1]

BY SIR LEONARD HILL, F.R.S.,

AND

SURGEON LIEUTENANT-COMMANDER A. E. PHILLIPS, R.N.

ROBERT BOYLE, after inventing the air-pump, submitted animals to evacuation (1670) and observed a bubble of gas set free in the eye of a viper. He suggested that bubbles so set free might stop the circulation.

Some fifty years later Halley contrived a diving-bell efficient for shallow work, and a helmet which he used for getting out of the bell.

It was not till 1857 that Hoppe-Seyler, repeating the evacuation experiments of Boyle and observing bubbles of gas set free in the blood-vessels of a rabbit, gave a correct explanation of the cause of "caisson sickness" which had resulted from submarine work at greater depths.

The experimental proof was finally given by Paul Bert in "La Pression Atmosphérique" (1878); he found that bubbles appear in the blood when decompression is too rapid in relation to the compression and its duration; these bubbles, by interfering with the circulation in one or other part, cause "bends," paralysis, and even death. Bert's work was, however, not recognized in this country by submarine engineers or their medical advisers.

In Allbutt's "System of Medicine" (1st Edition), diver's palsy was attributed to the mechanical effect of pressure on the circulation. It was not realized that the human body is practically incompressible, and that changes of atmospheric pressure are equally borne by, and transmitted to,

[1] The greater part of this article formed the subject of a paper read before the United Services Section of the Royal Society of Medicine on December 14, 1931, and is reproduced by permission from the *Proc. Roy. Soc. Med.*, vol. XXV, p. 693.

all parts of the body; that as the diver descends he is submitted to gradually increasing water-pressure, and this is exactly counterbalanced by the pressure of the air pumped into his suit. The diver therefore breathes air at the same pressure as that of the surrounding water.

In 1900, Leonard Hill disproved the erroneous view by enclosing an animal, suitably anæsthetized, in a chamber together with a manometer to record blood-pressure, and then rapidly raising and lowering the pressure by 15 lb. per square inch. No significant concomitant change appeared in the record. Further, he enclosed a frog in a small chamber fitted with a glass window at either end, and spread the web of the frog over the inside of one window, so that when illuminated by an arc-lamp the circulation in the capillary vessels could be observed with the aid of a low-powered microscope.

On quickly raising the pressure by 10 to 20 atmospheres no changes were noted in the even flow of blood along these delicate vessels. The increased air-pressure causes an increased solution of air in the blood and body fluids, in accordance with the law of partial pressures, but time is required to convey the dissolved gas from the lungs to the tissues and saturate these.

Thus, after keeping a frog in highly compressed air for some time and then rapidly decompressing the animal, bubbles of gas were seen to appear in the capillaries and stop the circulation. On recompression, the bubbles were observed to shrink until the circulation became re-established. The cause and cure of compressed-air sickness could thus be projected as a demonstration on the screen.

Major Greenwood and Leonard Hill, in 1905, after preliminary observations on cats, dogs and monkeys, submitted themselves to compressed air in a chamber provided by Mr. R. H. Davis, of Siebe, Gorman and Co., Ltd. The highest pressure reached was 90 lb. per square inch (7 atmospheres absolute). It was shown that diving could be carried out safely to a depth of 210 ft. The method of decompression used was a uniform one, about twenty minutes being given for each atmosphere.

Soon after the publication of these experiments, the *stage* method of decompression was put forward by J. S. Haldane, designed to lessen the amount of saturation of those tissues with the slower rate of circulation and occasion the highest impulsion compatible with safety for the escape of dissolved nitrogen from the blood into the lungs.

Analysis had shown that the gas set free by too rapid a decompression is mainly nitrogen, and that while the watery tissues, when saturated, dissolve about 1 per cent. of nitrogen for each atmosphere of pressure, the fat dissolves 5 to 6 per cent. and is therefore a great source of danger to workers in compressed air.

It has been pointed out by Leonard Hill that a great source of danger during decompression is the expansion of the gas which is swallowed or formed by fermentation in the alimentary canal.

Any gas formed while the diver is, say at a depth of 300 ft., i.e., 10 atmospheres pressure, will expand on decompression to ten times its bulk. Such gas extending the gut under pressure may pass possibly into the capillaries and start bubbling, either directly or by diffusing into the blood.

Guinea-pigs and goats fed on green food were shown to be liable to die from a decompression rate which was relatively safe for fasting animals. It is wise, then, that only a light breakfast should be taken before deep diving, and that a diver should be tested to be free from excessive "wind in the guts."

The Tables of Decompression used by the Admiralty were established by the 1907 Committee, based on experiments on goats carried out by J. S. Haldane, A. E. Boycott and G. C. C. Damant, and have been used successfully.

The use of oxygen for hastening decompression, suggested by Paul Bert, was tested by Leonard Hill in 1912. He measured the amount of nitrogen simply dissolved in the urine which he passed, (1) when exposed to compressed air, (2) when breathing oxygen in the chamber at the same pressure. The results showed that breathing of oxygen rapidly eliminated the nitrogen dissolved in the urine, which came of course from the blood circulating through the kidneys.

In collaboration with Mr. R. H. Davis there was designed, before the Great War, a submersible chamber for divers to enter and be decompressed in; the use of oxygen breathing within this chamber was proposed. Observations of Bornstein had shown that it was safe for men to breathe oxygen at 30 lb. pressure (3 atmospheres absolute) for thirty minutes. A longer time than this, or shorter times at higher pressures, were dangerous owing to the fact that convulsions are produced by acute oxygen poisoning.

It had also been shown by Lorrain Smith that prolonged exposure to concentrations of oxygen, even at only one atmosphere of pressure (absolute), produced pneumonia.

The experiments made by Paul Bert and Leonard Hill on animals and by Bornstein on men showed, however, that there was no danger in breathing oxygen during decompression in the stages downward from + 30 lb.

As the depth of breathing and the rate of circulation can be greatly increased by exercise, Major Greenwood and Leonard Hill had used this means of ensuring the safety of decompression in their own case.

In the Hudson Tunnel, Japp arranged for the decompression to take place in stages, and ground had to be walked over and steps climbed by the men between the stages. He reduced the period set by the Admiralty table by one-half, and the men thus exercised escaped with very little caisson sickness—a most significant result tested upon some thousands of working shifts of many individual men.

It was evident then, in 1912, that the times given in the Admiralty

tables could be greatly shortened by exercises and by breathing oxygen during decompression.

Nothing, however, was done until Mr. R. H. Davis, in 1929, actually produced a new and simply designed submersible decompression chamber. This chamber, together with the "Salvus" oxygen-breathing apparatus, was used in the Admiralty tests, made in collaboration with Messrs. Siebe, Gorman and Co., in 1929-31.

To test further the effect of breathing oxygen, Argyll Campbell and Leonard Hill (1929) measured on themselves the rate of "washing" out of dissolved nitrogen from the body produced thereby, and found that about one-third of the calculated amount in the body is rapidly got rid of; the rest comes out slowly, owing to the partial pressure of the dissolved nitrogen in the blood sinking to a level very little higher than that of the small amount left in the lungs.

This is because the diffusion of nitrogen into the blood from the parts with a slow circulation (e.g., the fat) is slow. The conclusion reached was that while the nitrogen dissolved in the blood which might cause dangerous bubbling in the heart is rapidly got rid of, decompression must be sufficiently prolonged and oxygen breathing kept up in the last stages from + 30 lb., so as to prevent any bubbles forming in the central nervous system which might produce paralysis, or in the peripheral nerve endings which might produce painful "bends."

H. E. Soper calculated that the use of oxygen might halve the Admiralty decompression times. The time taken in bringing a diver to the surface who has been working at a depth of 204 ft. for one hour is 124 minutes, a very considerable waste of working time, difficult to carry out if the weather changes, and a considerable feat of endurance if it is considered that the diver is hanging on a rope, suspended in mid-water, often at a temperature of 40° to 50° F., and in a strong tideway.

The use of the D.S.D.C. (Davis submersible decompression chamber) with oxygen breathing and exercises, makes the period of decompression shorter and far more comfortable; it enables the diver to work at greater depths, and to be brought up immediately and safely to the surface in case of emergency.

In 1929, the Admiralty conducted some experiments with the German deep-diving suit, in which the diver works at ordinary atmospheric pressure. The comparative immobility and difficulty in keeping the joints watertight precluded its use for rapid skilled work such as is required for saving the life of men entombed in a disabled submarine.

An observation chamber has been used by the Italians in their attempts at saving bullion from the *Egypt*; the diver within this telephones such instructions as are necessary for the placing of demolition charges and grabs, to the surface.

Such a chamber, which was originally designed by Messrs. Siebe, Gorman and Co., can be rapidly raised and lowered; it enables much pre-

liminary observation work to be done, and preparations made for the diver in the ordinary suit to complete rapidly any skilled work, such as requires the use of the hands.

In the months preceding the 1931 diving trials, Mr. R. H. Davis arranged for Captain G. C. C. Damant, R.N. (Retd.), to calculate a complete new set of decompression tables up to 300 ft. depth, on J. S. Haldane's system, taking into consideration five groups of tissues saturating at different rates, and allowing for the accelerating effect of oxygen, breathed from a certain point in the decompression scales. Mr. R. H. Davis placed his experimental plant and other facilities at the disposal of the Admiralty for the purpose, and several hundred tests of these tables were made on goats, in the course of which it was found necessary to increase the safety factors largely, the system of calculating remaining the same. Eventually a coherent decompression emerged which had been thoroughly tested over the range in which our men were to dive, and the success of the deep-water trials about to be described was largely due to this careful and systematic preparatory work.

What Knowledge have we Gained by the Work of the last Three Years?

Investigations are still proceeding and much work remains to be done, but it is considered that sufficient knowledge has been gained to permit preparations to be made for the routine training of a proportion of our divers for deep-sea work. It is hoped that later, deep-sea-diving sections will be attached to our principal fleets at home and abroad.

The use of oxygen-breathing during decompression and the use of the D.S.D.C. have made diving more safe and the time spent during decompression more comfortable.

Diving and working at a depth of 300 ft. in a rubber suit is both safe and practicable. Actually one of our divers has reached a depth of 344 ft. and came to the surface as you and I would return from an afternoon walk.

The use of oxygen-breathing during decompression has effected a saving of from a-third to a-half of the total time spent in decompression, a valuable gain both from the point of view of the diver and the officer in charge of the salvage.

Exposure of animals to 45 lb. pressure of oxygen soon led to convulsions, and the quicker the pressure rises the quicker is the onset.

No case of oxygen poisoning has occurred among the divers. They state that after their dive, when they climb into the D.S.D.C. and commence breathing oxygen, they feel very refreshed. The increased concentration of oxygen may account for their feeling of fitness on the bottom, since when breathing atmosphere air at a depth of 300 ft. they are exposed to two atmospheres of oxygen.

The exposure of one diver for 88 minutes to oxygen at an average pressure of two atmospheres produced no evil effects.

At the end of three months diving there was a slight diminution of lung fibroses in all ten divers. In one case functional albuminuria was prevented by the use of oxygen.

What Standard of Fitness has been Regarded as Essential for Deep-Sea Diving?

Except that the diver should be possessed of a very stable mentality, our experience does not suggest that it is necessary for the deep-sea diver to be any more fit than a diver engaged in shallow water.

Volunteers for deep diving should have had over two years' experience in shallow water diving, and be under the age of 30.

While deep diving was in the experimental stage, to be on the safe side, only the very fittest was chosen. This was partly to ensure that if the work proved to be very arduous, that the divers would have the necessary stamina to stand up to it, and partly to eliminate all such as were subject to illnesses which, if they occurred during the trials, would prevent their diving. From the information which has been gained it is hoped to be able to reduce the standard of fitness now that routine training has been instituted.

Previously the thin, spare type was regarded in our Navy as most suitable for diving. Experiments carried out by Argyll Campbell and Leonard Hill on the rate of saturation of the marrow-fat in goats submitted to compressed air, indicate that for short exposures the fatter animal will be less saturated. Fatness may be an advantage for short periods and most disadvantageous for long periods. The thin type does not seem always to have the same physiological and psychological reserves. Subcutaneous fat is required to protect against the cold.

The entrance medical examination was mainly directed to the obtaining of a stable heart, labyrinthine system and healthy lungs. This, and the subsequent tests of the selected divers were carried out by one of us (A. E. Phillips). The preliminary examination was similar to that employed by the Air Ministry, and thanks are due to them for their assistance, and especially to Wing Commander H. A. Treadgold, R.A.F.

Some of the candidates accepted had one defect, but this was only permitted if it was not considered likely to produce an adverse effect on the diver.

In actual practice one of the divers had a well-marked hyperpiesis, but he came through the season just as well as the others, and actually was much healthier afterwards than before; his blood-pressure at the beginning of the season was 143 and 93, and at the end of the season, 132 and 80.

One test which was used consisted of touching the toes with the fingers 250 times in ten minutes, and to be satisfactory, the pulse-rate should not

exceed 130 on completion and should return to within 10 per cent. of the pre-test rate in twenty minutes.

One diver, after this test, was found to have his urine loaded with albumin. When the test was repeated and oxygen was breathed instead of air, no albumin could be detected. The test was carried out thirty-seven times in six months, and the answer was always the same in the case of this diver. Renal-efficiency tests suggested that this was a case of functional albuminuria.

Some other cases suffering from this complaint have had similar tests carried out on them, and in every case the amount of albumin was diminished by the use of oxygen, or eliminated altogether.

Another test employed, which is not in general use, was a mental excitability test, which was a modification of a similar test invented by a Japanese worker. The test consisted of placing small strips of blotting paper, treated with carbol fuchsin and mounted on plaster, on to the palm of the hand, while a control strip is placed on the chest near the axilla.

The test relies on the assumption that sweating of the palms is due to mental excitement or pain, and is not due to heat. The result was considered positive if the stain left on the palm was about twice as pronounced as the stain made by the control. The test gave moderately accurate results.

Value of Certain Medical Tests and Results Obtained.

The trials have afforded an opportunity for exhaustive and continuous application of certain tests. Further, they were useful in supplying what must be regarded as something approaching the optimum figures for the tests, for what with the rigorous medical excluding examination and the healthy lives they lead, it would be difficult to conceive a more healthy body of men.

At the initial medical examination a very large number of tests were applied, not so much as a means for the exclusion of the candidate as for throwing light on the efficiency of the test for separating likely successful from unsuccessful divers; and in order to obtain this information, blood-pressures, pulse-response tests, 40-millimetre tests, balancing and labyrinthine tests, and vital capacity tests were applied daily, both before and immediately after diving.

As is to be expected, daily variations were always present and existed during different times of the day, but they were slight.

Towards the end of each diving week, blood-pressures were on the up-grade and vital capacities falling—all very slightly. The long week-ends generally restored the levels to par, but the same tendency could be observed at the end of the three months' diving season, especially as regards the diastolic pressure. Incidentally, those with a slight hyperpiesis showed the better stamina.

We attach great importance to a stable labyrinthine system, since the diver may be called upon to work in bad lighting conditions. With regard to the 40-millimetre test, contrary to the usual experience, the holders of the best records for the test showed the least desire to hold out under unfavourable conditions.

With one breath to hold a column of mercury at 40 mm. for 2 min. 23 sec. is almost phenomenal. This diver exhibited wonderful powers of endurance in achieving these figures, but his powers of endurance on the bottom were strictly limited. Psychologically he was not so stable, and it may have been something in this direction which hampered him when diving. This diver had five attacks of " bends," and because of this had to be removed from the deep-sea diving list.

Very little difference could be detected in the figures obtained before and after diving. One noticeable after-effect of diving was an almost overwhelming inclination for a nap an hour or two after diving. This tendency was seen also after compression in the experimental chamber at Siebe, Gorman's.

The heart condition of the diver, when working and at rest on the bottom of the sea, was studied by means of a microphone fixed over the apex of the heart, which was connected through the diver's helmet to an amplifying set on the surface, and to a loud speaker or headphones. It could be connected to a telephone on the desk of an Admiralty office.

By means of this device it was found that a diver, when performing a piece of work on the bottom, had an increased pulse-rate of only five beats per minute. The small increase is attributed to the influence of oxygen, for the diver was breathing air with oxygen the equivalent to two atmospheres of pressure.

Another device is intended to measure the respiratory rate of the diver; it consists of an electric belt worn round the thorax, which is connected through to the surface to four electric bulbs. The device is so arranged that, at rest, bulb 1 lights on inspiration and dims on expiration; under working conditions bulbs 2 and 3 are illuminated depending on the depth of inspiration; bulb 4 means maximum expansion.

On Returning from a Spell of Work at 300 ft.

The diver is as fit, and often fitter, than when he went down. Diver after diver has said the same, and their statements are substantiated by the records. To quote an actual case at random : Blood-pressure before diving, 123 and 79 ; after, 116 and 85. Forty-millimetre test before diving, column held suspended for 62 seconds; pulse-rate per 5 seconds, 7, 6, 7, 6, 7, 6, 8. After diving, column held suspended for 64 seconds; pulse-rate, 6, 6, 6, 6, 6, 7. Pulse-rate resting before dive, 74 ; after the dive, 72. Pulse-response test before diving : pulse on completion, 116 ; at the end of one minute, 92 ; after diving, 108 and 82. Vital capacity before diving, 5,250 ; after diving, just the same.

Possible Dangers Peculiar to Deep Diving.

More care is necessary to prevent the diver coming to the surface too rapidly, since he is more heavily charged with nitrogen.

The danger-zone when oxygen poisoning is expected is more nearly approached, but so far no cases have been encountered.

Carbon dioxide requires attention, since 1 per cent. in the helmet on the surface will give a partial pressure of 10 per cent. at 300 ft. We had one mild case this summer.

Slight attacks of giddiness may be experienced on the bottom; this we believe in most cases—in one we have positive proof—to be due to the diver descending too rapidly, and by not equalizing the pressure of air in the middle ear reflexly excites the labyrinthine system.

One diver in 1930 unfortunately died from complications following an attack of caisson sickness. Psychological conditions, presently to be described, probably played a contributory part in the production of this sickness.

The caisson sickness encountered in deep-sea diving in no way differs from the forms manifested in the shallower diving or tunnel work, and it cannot be too strongly stressed that the cure for it, whether caused in tunnelling or shallow or deep diving, is the same, that is, immediate and adequate recompression. No matter how serious the case, if recompression is properly carried out, the treatment should succeed.

Even where decompression is greatly at fault, recompression will save the case; especially is this so where the D.S.D.C. is used, for the diver is under observation, and treatment greatly facilitated. This year in deep diving, we had sixteen cases of "bends," that is, an extremely painful manifestation of caisson disease, caused by a bubble in a sensory nerve or nerve ending.

These cases were all cured by a recompression pressure of a few pounds. Of these cases, five occurred in the same diver; it has been observed that some are much more prone to caisson disease than others. The idiosyncrasy of this diver to the disease, as has already been stated, has necessitated precluding him from further deep diving.

It seemed to us that these "bends" were more liable to occur on damp days than on fine; it is certain that where divers suffer from a neuritic-like after-affect, that these attacks always coincided with wet weather. For cases occurring after leaving the D.S.D.C. a large recompression chamber was available.

Oxygen breathing was carried out during recompression, and here, as in decompression, an appreciable saving of time was effected. The recompression chamber is comfortable; the diver has one or two attendants and can indulge in reading or cards during the lengthy process of recompression.

During the 1930 season, when working, or in many instances resting, at 270 to 300 ft., some of the divers experienced what to them were new

sensations; they found that it was much more difficult to assimilate facts and to exercise that quick decision which is so essential for successful diving. It might be summed up as a slowing up of the process of cerebration.

Some of the divers went a stage further than this, for when they returned to the surface they stated that they had "passed out" when on the bottom. It was known that if this was so, it could not have been for long, for they had answered by their telephone the instructions they were continually receiving.

Others of the divers stated that they had experienced a detached feeling, as if they were under an anæsthetic. Another diver said, when asked to describe deep-sea diving :—

"You notice the dark more although it may not be darker; the light is a comfort and company. You notice things more if there is nothing to do; I get comfort from seeing the fish, it takes your mind off everything else."

This diver also had patchy loss of memory; his main statement is more a history of state of tension of mind, but it is valuable inasmuch as it shows that in 1930 a state of tension existed, in some of the divers at any rate, whereas in 1931 we failed to get any evidence of its existence.

Another diver stated that he "came over funny" in deep water, and said : "You get keyed up in deep water"; he also had some difficulty in remembering the work he had done.

When asked for a description, an old hand at diving gave the following account : "You have to be more careful in deep water; in deep water you know that you are concentrating." He described how you think of each heave as you turn a spanner. He said : "If you go down with a set purpose it becomes an obsession; it will become the main thing and you will forget everything else." He described how he thinks very deliberately; he says, "I have finished my job, what shall I do next?—of course I have finished and now I must go up." He described how he was aware of every action : "If my hand goes out I think of my hand going out." He gave the following as an analogy : "If I saw a thing of value, say half-a-crown, in the street, I would pick it up. Down below I would look at it and think, 'What is that, shall I pick it up? Yes, I will pick it up' and then I feel my hand go out."

The latter account is about the best description of how most of the divers felt in 1930 when between 270 to 300 ft. Some felt it less, others more.

With two exceptions all the divers looked and felt fit when they returned to the surface. The exceptions were white-faced and "windy" when they came out of the D.S.D.C.; these two were regarded as unsuitable for further deep diving.

These accounts which the divers had given had to be sifted, and action taken to discover what could be the cause of their loss of memory. Sir Leonard Hill, who had noticed symptoms in the 1929 divers, was of the opinion that the cause was mental and not physical.

The Admiralty Deep Diving Committee asked for and obtained the assistance of the Medical Research Council in investigating these new disorders, Dr. Culpin being appointed by the M.R.C. to investigate the problem.

From the description given to him, he considered that these symptoms were more likely to be expressions of a mental than a physical disorder, and he stated that he had met with a similar condition of so-called loss of consciousness in cases of shell shock. It was arranged that the divers should be sent to Dr. Culpin for an interview.

As a result of these interviews Dr. Culpin reported that, with three exceptions, the divers were free from symptoms. Two of the three exceptions were the divers who had, as a result from their experiences on the bottom, been made unfit for further deep diving.

With these two Dr. Culpin succeeded in restoring missing pieces of memory ; the third exception had only had a very slight loss of memory; the same method which had succeeded with the other two men was employed, but the endeavour to piece his memory together failed in this case : the diver was permitted to continue diving, and this year was regarded as our most successful diver and did not feel any abnormality.

The following is an account of one of these divers who arrived at the surface looking blanched and "windy" and was excluded from further deep diving : this was one of the divers whose losses of memory Dr. Culpin succeeded in restoring. For these notes we are indebted to Dr. Culpin.

The interview was directed to obtaining two different kinds of information : part one was to obtain an insight to the psychology of the diver, and part two was to restore, if possible, the missing links of memory.

The detailed account which the diver gave when in a mildly hypnoidal condition warranted the assumption that his memory had been restored. Regarding his own psychology, the diver volunteered the following information :—

"I don't like to attract attention, nor would I care to go alone into a teashop which I did not know, for I would feel that everyone was watching me; I would rather go hungry. Discipline irks me, I am afraid of doing the wrong thing, I often have the feeling of being watched, it affects me when in charge of strange men. I keep to myself, and, I am afraid, sometimes worry about what others think of me."

As a child he dreaded his father. Coming nearer to the events which affected his diving, he said :—

"I never remember being afraid of the dark but I have always been afraid of enclosed spaces. I get a feeling of being sealed in, in these places."

The terror (his own words) came on first when skylarking with others ; he found himself at the bottom of the scrum, nearly suffocated.

He was once, as a child, thrown into the sea, and since then he has not liked it, and although he has passed his swimming tests, he does not like going out of his depth.

As a diver he was frightened of making mistakes; the old fear of being closed in came back to him in Scotland; he said: "It had not worried me for a while, but it came on that time just before I went off—on the bottom; that stirred it up, and I have had it ever since." He then proceeded to describe his deep diving in Scotland in 1930.

"I felt dizzy at 240 ft., and at 270 ft. I felt just like being in a nightmare; it felt like going under ether; I think that is what made me think of going unconscious. I had a feeling of being closed in and went off. I did not tell them what I have told you, I just said that I had been unconscious. On that occasion I felt tingling in my limbs and I thought that the heavy pressure was crushing me into my suit. I thought that if ever I get out of this I'll never dive again. After this I cried off deep diving, but I thought it over and afterwards asked to be allowed to carry on." The description of his last dive, which was at 300 ft., was as follows:—

"I left the ladder determined to get to the bottom; at 250 ft. I got a recurrence of the tingling and a feeling of lying on my back. I decided to rest a couple of minutes and then go on. I slid 10 ft. and felt I was going unconscious. I made signals to be pulled up and kept repeating them. I lost the use of my limbs and let go everything. While hanging on to the shot rope I saw my own face in the front glass; it was outside the glass and looked all greenish; I was dressed in my shore-going suit. I heard the order, 'Pull the diver up,' again and again, as if someone in the suit was saying it. When I got to the D.S.D.C. I did not appreciate the oxygen as usual, I wanted fresh air."

At the interview with Dr. Culpin in London, he was placed on a couch, with closed eyes, and directed to go over the descent "as if it was happening now." With some urging he repeated the performance, and seemed to recall the whole of the period for which he had claimed to be unconscious.

At one stage of the narrative he cried out: "Pull me up, for God's sake pull me up. I feel as if I'll never get up. I'm tied on the bottom, my mouthpiece is caught under my nose. It is getting lighter now, I can see the chamber."

Then he was made to sit up and tell the story again. This time he gazed straight ahead, and talked as if he was still going through his experience, and he was able to add a few details to the first account: "I felt that I was being pulled up against resistance, as if a fellow was trying to hold me down; I am fed up and want to get out—worried because I can't open my by-pass; I seem to take two minutes trying to open it."

In the talk which followed he agreed that actual incidents he had forgotten had now come back to him.

It was decided that this diver and the other who had been under suspicion were not sufficiently stable for further deep-sea diving. It was arranged that an interview designed to look for symptoms should be

included in the medical examination for deep-sea divers in H.M.S. *Excellent* and that those passed should be further examined by Dr. Culpin. In this way it was hoped to exclude those with mental instability, and thus to prevent the losses of memory which had made notable the 1930 season.

Ten divers for the 1931 season were examined and passed as free from symptoms, although the tenth was only passed after consultation between Dr. Culpin and myself.

The first nine divers did not encounter anything of an abnormal nature and no loss of memory or any other unusual sensation was recorded during this diving season. Most of them however did, when in the experimental chamber at Messrs. Siebe, Gorman's, at an air-pressure equivalent to a depth of 300 ft., experience a momentary giddiness. If they were reading the print became blurred for an instant: this sensation was not repeated in Scotland when working at 300 ft.

The tenth, or suspected diver, developed an acute claustrophobia after seven weeks diving when he was at a depth of 270 ft.

He is of the suppressed, nervous type, and is one who habitually exercises self-control; this latter attribute he has developed to a remarkable degree. The other divers afterwards told me that he was rather inclined to "go off the handle" unexpectedly, and that he much disliked being the first diver to go down to an increased depth, or to be the first diver of the day. On the day that he broke down he was the first diver to go down.

He is only partially conscious of his own nervousness; for instance, he does not like going into the wardroom; if he is in uniform on shore he has a feeling of being watched, and more important, he was frightened of the dark as a child, and even now is very frightened of horses; nothing could induce him to pat a horse.

In reply to the questions as to certain of his mental speculations, he admitted, "I often think of where I come from, but I must not *talk* of it or they would think I am qualifying for an asylum."

A history such as this would seem to point to mental instability, but apart from these peculiarities—and they are, or certain of them are, possessed by many of us—he appeared to have a very equable temperament, and the deciding factor in accepting him was his splendid physique.

During the chamber tests at Siebe, Gorman's, he gave a strong positive reaction to the mental excitability test, but he insisted that he had not felt anything unusual. After the breakdown he confessed that he had felt queer on one occesion. When asked if the feeling had been similar to that immediately preceeding his breakdown, he said: "You cannot possibly compare the two conditions; in London, in the chamber, it was light and there were others with me; on the bottom it is dark and lonely."

While he was diving in Scotland he was kept under as close medical observation as possible without arousing suspicion.

On one occasion his pulse-rate on the bottom was much too fast for the

work which he was doing, and, from his conversation on the telephone, which sounded very artificial, it was suspected that he was not altogether happy. Removal from the trials seemed too drastic a procedure, as the suspicions were based on small evidences.

It was after he had been on the bottom for six minutes at 270 ft. that he urgently demanded to be brought up, giving no reason but just constantly repeating his demand; he did not appear to be in a panic but was most imperative in his request; right up to this he had been conversing on the telephone and giving directions to the surface regarding the hoisting or lowering of wires connected with his work.

Great difficulty was experienced in making him remain at his decompression stops; his one desire was to "blow everything" and get at least to the D.S.D.C., if not to the upper deck; the chamber was specially lowered to a greater depth than is usual to comply with his request.

The chamber attendant reported that, on his arrival in the chamber, he looked normal except for being very white and having a glassy look about the eyes. During decompression he became more cheerful and tried to describe what had happened on the bottom. He said, "Have you felt that you would like to murder a 'so-and-so'? Well that is what I felt like on the bottom when I 'came to' and found myself trying to unscrew my front glass; my one idea was to get out of the helmet and into the chamber."

When he emerged from the D.S.D.C. he seemed like one who has sustained a severe mental shock; his ocular appearance and whitened face supported this impression. Physically he was badly shaken, but no worse; he was overcome by the situation and deeply self-conscious of failure—indeed, the main difficulty in restoring him was to overcome this idea; he was striving desperately to recover his self-control. He could not bring himself to recount his experiences verbally, but agreed to write them down. The following extracts are from his own written statement:—

"I was at the time kneeling on my right knee and head down (the required position for putting the clips on the door) when suddenly I came over rather 'funny'; it was a distinct 'different' feeling; I stood up, the tank wire in my right hand, and thinking it was a touch of CO_2, I began to breathe deep and hearty, thinking of course that in a couple of minutes I would be able to resume work. Then I seemed to go quite limp, a feeling of 'no life or energy'; this was new and strange to me, whether it was a part of CO_2, I didn't know, because I have never experienced a real dose of CO_2; anyhow, after stopping and doing the drill for CO_2 I thought I would be alright, but suddenly something definitely seemed to—say—snap inside my head and I started to, what I thought, go mad at things.

"I had small laps of this, on and off. Breathing became difficult, possibly I might have asked for more air, I couldn't say for certain. I really did try, and fought hard to beat this feeling of madness, but it seemed all of no avail. I didn't get worse, but such as it was, it was quite enough for me. I wasn't in a real panic, and ready to do anything that came to

hand, although I did make a hash in some things. Anyhow, my one ambition at that moment was to get my helmet off, the quicker the better. I fought hard to stave off this feeling but it simply wouldn't go. I should say that unless one had had experience of this kind of thing, it would be very difficult to realize or imagine such. I felt slightly relieved when, after closing my ejectors, I left the bottom.

"After going say, 30 to 40 ft. up, I came to the conclusion that I was coming up a wire. I stopped and I was pretty well O.K. I thought to myself why I should think so, I suppose it was for the simple reason that the shot rope is the shot rope, and every diver knows what it is, and that I was going all wrong.

"Naturally in that moment of—say—recollection, I decided, although much against my inner feelings, to go down the wire and leave the bottom a bit like a diver is expected to. Down the wire I went and arrived on top of the tank, slid off and stood up. I don't remember how I actually left the wire and got to the shot rope, anyway I must have found it because I came up it.

"At this time, i.e., when I was standing at the foot of the shot rope ready to ascend, I was perfectly normal. I felt my ejector; was it already closed, or did I close it then? I can't remember, I did at any rate ensure it being closed before I left the bottom. I left the bottom, and during my ascent, can remember travelling 'light,' or I should say light at one period.

"Of course, as regards the phone, I was simply saying things that I wanted to, and was not interested in the answers. I say, not interested, but to take everything into consideration, I didn't look or wait for any answers, one may say that I was pure and simply giving orders.

"I had a check at — ft. I don't know, but at the time I dimly remember 110 ft., of course that being the check that coincided with the decompression tables. Since then I was told that it was 90 ft. I felt something happen on the shot rope and I guessed that it was the chamber being lowered to a depth that would be of some help to me, which afterwards proved to be correct. I received the check signal at 90 ft., and although I answered it, I really, inwardly, didn't want to. Once again my one ambition was to get either on deck or in the chamber and have the helmet and glass taken off.

"Of course now at the present moment I am alright, and as one might guess, I feel a wee bit self-conscious of myself, but still at the time I felt that I never wanted to be dressed as a diver again. After doing a check which was very short, presumably a minute, again I had a greatest of all fights to stop there and do it. I had the phone message to go to the chamber. Just above me was the chamber and I gladly got on the ladder, and although in such a 'paddy' and 'panic' with myself, I did try and do things as I always had done. I undid the front-weight lanyard and let them take the weight off, then I got secure in the chamber and got my front glass off. I didn't feel as happy as I thought I would, because things still

seemed in the same condition somewhat. It was a relief however to have the front glass off, and the helmet soon followed. While on the bottom I thought it would be absolutely good to have the helmet off, but when it was off I didn't feel as I have before.

"I told them that everything was O.K., because physically I was alright, and again my sense of self-consciousness came into play. But taking it all round, I just didn't have and couldn't display the usual amount of life that I had done on previous occasions.

"From then onwards I felt pretty well alright."

When he arrived on the upper deck he was on the verge of a complete mental breakdown. To keep his mind temporarily off the subject he was sent on shore with two of his fellow divers and given a full dose of alcohol.

The danger in his case was that he would attempt to suppress the incident and relegate it to his subconscious mind. To avoid this I persuaded him that night to recount verbally his experiences on the bottom.

Practically no hypnoidal effort was required to produce the horrors of that morning's dive, and the picture of stark, mad terror which even the interview could produce, left an impression which is very difficult to describe. The impression was of sitting in the stalls and watching the acting of a Grand Guignol. To such a pitch did he arouse his emotions that he clawed his face to remove the imaginary face-glass and tore his clothes which he mistook for his diving suit.

The production of any reaction produces as satisfactory a result as the surgeon's knife in abscess formation, and it was so in this case; from this onwards the dam was loosened and he was enabled to talk to the others of his experiences; previously he had refused to talk on the subject.

Since the incident, which happened in Scotland, two shallow-water divers were reported as being "windy." In each case I found the cause to be claustrophobia. One, who was fearfully particular about his air supply, as a boy had nearly been suffocated by a pillow in a pillow fight, and ever since had been terrified about not getting enough air.

To sum up briefly: These four failures in deep diving, and the two in shallow diving, have many points in common; they are of the suppressed nervous type, who habitually exercise control—shy, reticent and self-contained; they work best on their own and do not relish observation; they are usually of a philosophic, rather than a practical, disposition.

The most desirable method of selection to avoid this mental instability is a matter of opinion, but our experiences suggest that for the present such a state of mental instability, slight as it is, debars from deep diving.

Some advocate a very complete psycho-analysis, others preferring to rely on a very complete history of the diver from his first dive, coupled with close observation by instructors and officers, such observation being minutely recorded.

The latter method depends on skilled and accurate observations which must be carefully recorded, but when the observer and observations are

known, this is the method *par excellence*. At the time of these experiments this method of collecting facts had not yet been instituted, hence resort was made to the former method, which depends on an accurate forecast by an expert after careful study as to how the candidate is likely to react under given circumstances; these circumstances are mainly the darkness and loneliness which may be encountered on the bottom of the sea. We may add, in conclusion, that both darkness and loneliness are now largely mitigated by powerful arc-lamps, efficient telephones and observation chambers.

Reprinted from SCIENCE, July 21, 1950, Vol. 112, No. 2899, pages 91–92.

Hydrostatic Pressure Reversal of Narcosis in Tadpoles[1]

Under physiological conditions the narcosis of bacterial luminescence by alcohol, urethane, and certain other drugs may be virtually abolished by an increase in hydrostatic pressure (Johnson, F. H., Brown, Dugald, and Marsland, Douglas. *Science*, 1942, 95, 200). Experiments reported herein show that a similar relationship occurs in higher animals, viz., tadpoles of *Rana sylvatica*.

Young larvae, measuring 15–18 mm in total length, were placed in 3%–6% alcohol in tap water at room temperture, 22°–26° C. Both spontaneous activity and response to gentle mechanical stimuli ceased in a few minutes. The narcotized animals were transferred to a steel pressure chamber with Herculite plate glass windows which afforded an adequate view of the interior. The chamber was filled with the same narcotic solution, and pressure was applied from a connecting hydraulic pump. Pressures up to 1,000 psi had no apparent effect, but higher pressures, between 2,000 and 5,000 psi, varying somewhat in repeated experiments with different groups of individuals, caused reappearance of spontaneous activity almost immediately with rise in pressure, and the animals swam about in apparently normal manner. In luminous bacteria at optimum temperature, 3% alcohol causes about 50% inhibition of luminescence intensity, which is largely reversed under 5,000 psi.

[1] This report is based on studies aided in part by a grant from the American Cancer Society, through the Committee on Growth of the National Research Council, and in part by an institutional grant to the Department of Biology, from the New Jersey Section of the American Cancer Society, for fundamental biological research.

Similar results were obtained with tadpoles narcotized in 0.08 M urethane; this inhibition of luminescence is likewise reversed by pressures of the same magnitude.

In contrast, pressure did not reverse the narcosis of tadpoles in 0.001 M *n*-amyl carbamate. This result again corresponds to those obtained in current studies with luminous bacteria which indicate that the inhibition of luminescence by *n*-amyl carbamate, in approximately the same concentration, is scarcely affected by pressure.

Unnarcotized tadpoles became more active under 2,000 psi, but less active with further rise in pressure, and motionless at 5,000 psi. Other aquatic animals have been observed to behave similarly, and pressure itself has been viewed as a narcotic (Ebbecke, *Pflüg. Arch. ges. Physiol.*, 1935, 236, 648). In our experiments the reversal of drug narcosis was always manifested before harmful effects of pressure became apparent. Following compression at 5,000 psi, gradual recovery in tap water at normal pressure often occurred, but some of the individuals died. Narcotized animals that were not subjected to pressure always recovered after transfer to tap water.

The basic mechanism through which temperature, pressure, and various drugs act on luminescence has been considered at some length (reviewed by Johnson, *Adv. Enzymol.*, 1947, 7, 215). Heretofore, there has been no direct evidence that the same theory, specifically with reference to the influence of hydrostatic pressure on narcosis, applies in higher organisms, although other parallels have been found with reference to the influence of temperature. These relations support the general implications of the fundamental theory, and invite further study with various aquatic animals and narcotic agents.

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RESEARCH REPORT 3-60

PERFORMANCE IMPAIRMENT AS A FUNCTION OF NITROGEN NARCOSIS

PROJECT NS185-005 SUBTASK 5 TEST 12

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1 JUNE 1960

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NOTE: Also appeared in J. Appl. Psychol. 46:91-95, 1962.

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ABSTRACT

Navy divers individually performed air dives in a high pressure chamber for 40 minutes at a simulated depth of 100 feet. Each experimental session consisted of three phases: a measure of performance on choice reaction time, motor coordination, and conceptual reasoning at sea level in the chamber; three 12 minute periods at a pressure equivalent to 100 feet of sea water, during which equal time was allocated to each of the three tests; and a final measure during the decompression stop at 10 feet. All subjects had been trained to plateau level of performance before the experiment proper had begun. Statistically significant decreases in performance for all subjects on all tests were found, with the greatest decrement occurring on the reasoning test, least on motor coordination. Decreased performance occurred as the pressure increased and remained relatively constant with duration of exposure.

SUMMARY

PROBLEM:

The problems dealt herewith are threefold: (1) to develop a procedure which could determine whether performance decrement appears in divers at simulated depths as shallow as 100 feet; (2) to evaluate the relationship between the amount of decrement and the complexity of the task; and (3) to investigate performance efficiency as a function of duration of exposure at a constant pressure.

METHOD:

Ten subjects were trained to a constant level of performance in a choice reaction time test, a motor coordination test, and a reasoning test. The amount of impairment was determined as a function of increased partial pressure of nitrogen, equivalent to 100 feet of sea water.

FINDINGS:

The results indicated: (1) significant decrease in performance for all subjects on all tests when compared with their individual sea level efficiency; (2) a position relationship between degree of impairment and the complexity of the task; (3) an initial loss in efficiency as pressure is increased and this loss remains relatively constant with increased duration of exposure.

RECOMMENDATIONS:

It is suggested that further experimentation be directed toward a determination of relative impairment at varied depths, an evaluation of continuous performance of a single task at constant depths, and the amount of individual and group variability to be expected as a function of depth and duration of exposure.

ADMINISTRATIVE INFORMATION

Ref: (a) Telcon between Mr. M. J. Foran (BuShips Code 638) and LTJG G. M. Janney (EDU) on 6 August 1959.

By reference (a) the Bureau of Ships authorized the subject project and assigned project number NS185-005 Subtask 5 Test 12.

LTJG R. J. Kiessling, MSC, USNR, as senior author, executed all phases of this project assisted by Clinton H. Maag, Ph.D., Assistant Head of the Physiological Psychology Branch of the Office of Naval Research.

The original outline for this work was submitted 27 July 1959 and approved by BuShips 6 August 1959. Actual experimental work commenced on 8 August 1959 and was completed 15 January 1960.

Estimated manpower requirements were as follows:

DESCRIPTION	MANHOURS
Planning	200
Testing	250
Reduction and Analysis of Data	150
Reporting	100
Clerical	30
TOTAL.....	730

This report is issued in the Experimental Diving Unit Research Report series and is the first report written under project number NS185-005 Subtask 5 Test 12. Charges incurred in the execution of this project were lodged against allotment 70102/60.

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1. INTRODUCTION

1.1 General

1.1.1 Exposure to high partial pressures of nitrogen produces a condition known as nitrogen narcosis. The condition is characterized by central nervous system depression, motor incoordination, euphoria, defective vision, and auditory disturbances. Reported also as symptoms are loss of judgement, fixation of ideas, and general slowing of mental activity.

1.1.2 It is evident that with the advent of the Scuba diver, nitrogen narcosis has taken on new prominence. Without surface communication or supervised control, the probability of lethal mistakes by narcotic Scuba divers is high. It is now possible that small otherwise unnoticed symptoms of narcosis may exercise an extremely significant role for this type of diver. It is not inconceivable that increased underwater dexterity and quicker reaction time will be a necessity in the fields of underwater ordnance and demolition. A high degree of judgement and reasoning power is essential in all phases of diving; anything less constitutes a potential hazard to a diver's safety.

1.2 Background

1.2.1 Since 1903, when Hill and McLeod (10) first published a report on the subject of nitrogen narcosis, various definitions and descriptive accounts have appeared in the literature. Rashbass (21), of the British Royal Naval Physiological Laboratory, states "nitrogen narcosis is the term which has been applied to certain changes in personality and performance in men subjected to increased pressures of air". Behnke (1,2) describes the condition as "an alerted mental state induced by breathing atmospheric nitrogen under pressure". Case and Haldane (8) refer to the condition as "a form of intoxication as much as a form of narcosis, with a tendency toward laughter and overconfidence, some loss of clear thinking, and very rarely hallucinations and mystical states". The diversity of these definitions, ranging from Costeau's (9) purely subjective description of "rapture of the depths", to experimental investigations of physiological changes and performance impairment, reflect the interest of the various authors and the particular segment of behavior observed.

1.2.2 At greater than atmospheric pressures nitrogen acts as a central nervous system depressant. The narcotic effect may range from mild euphoria to complete unconsciousness. Consequently, nitrogen narcosis cannot be adequately defined in terms of behavior manifestations without specifying the degree and duration of exposure. Adequate measuring instruments are therefore warranted to facilitate quantitative definition and to determine degree of decrement.

1.2.3 Speculation concerning the physiological basis of nitrogen narcosis is just as varied as that concerned with behavior modifications. One of these physiological theories (7) implies that the high partial pressure of nitrogen inhibits synaptic transmission and consequently

impairs central nervous system activity. Another explanation (11) attributes the anaesthetic effect to decreased metabolism at the neurocellular level. That is, because of the high nitrogen concentration the efficient utilization of oxygen in brain metabolism is inhibited. Since the pronouncements of Lindsley (12) and Moruzzi & Magoun (19), regarding the function of the reticular system as an "alerting or wake center", all sorts of impaired alertness, via drugs, lack of sleep, etc., including nitrogen narcosis, have been laid at the doorstep of the reticular activating system. Research is currently underway which should provide increased understanding of the physiological activity underlying nitrogen narcosis.

1.2.4 Although nitrogen narcosis has been recognized for at least the last fifty years, and considerable research data are available concerning physiological reactions under nitrogen narcosis, there have been few psychological studies of performance decrement. There are perhaps two reasons for this situation: (1) tasks required of the divers were of a simple mechanical nature and investigators were primarily interested in rather gross measures of human performance; (2) the primary research concern has been with the physical well-being of the diver. The few psychological studies that have been conducted were often without adequate controls and measuring instruments, since these data were often collected as a byproduct of experiments designed to provide physiological information.

1.2.5 Performance tests that have been utilized to study human impairment under nitrogen narcosis have been limited to relatively simple tasks, such as crossing out letters in a sample of prose, gross motor skills, typing, or well practiced intellectual tasks such as multiplication of two digit numbers. Shilling (23), in 1937, used arithmetic scores, cross out numbers, and reaction time to light. Case and Haldane (8) utilized arithmetic scores only, as did Rashbass (21) in 1955. Such simple tasks, particularly when accomplished with pencil and paper, merely measure one's memory of the multiplication tables. That is, a task which has been over-learned and which is engrained as a habit pattern is nothing more than rote memory. Measures of rote memory are notoriously poor indices of behavior impairment under stress. The same might be said of tasks which merely require the subject to cross out certain specified letters or numbers from a typewritten page. Rosenberg and Ramsdell (22) attempted the use of more complex measuring instruments, such as the "Porteus-Maze", "Goldstein-Scleerer Test", and Digit Substitution. Although these tests demonstrated decrement as shallow as 100 feet, conclusions reached could not be free from learning factors present in these instruments.

1.2.6 Among the most carefully controlled studies have been those conducted at the Royal Naval Physiological Laboratory. Bennett and Glass (3,4) of that institution utilized the appearance of alpha wave blocking and variation in Critical Flicker Fusion (CFF) as indices of nitrogen narcosis and correlated these with impaired performance. These studies are highly important in terms of our knowledge of the influence of nitrogen narcosis on nerve tissue and the visual sensory system, and may provide needed insight into the mechanism of action through the reticular system. The emphasis of this work is the establishment of

an index of critical threshold concentration and the authors postulate the inverse square law, i.e., the length of time for the concentration of nitrogen to exceed critical limits is inversely proportional to the square of the pressure. The curve expressing this relationship indicates that narcosis will appear after about three minutes exposure at a simulated depth of 200 feet of sea water and after about twelve minutes at 100 feet. These studies indicate that performance impairment does not appear until after the critical threshold has been exceeded as evidenced by alpha wave blocking and raised CFF threshold. Therefore, also of significance is the nature of decline in performance at a constant partial pressure of nitrogen as a function of duration of exposure.

1.3 Research Implications

1.3.1 A systematic analysis of performance under conditions of nitrogen narcosis is of significance from both the theoretical and applied point of view. Theoretically an analysis of behavior under nitrogen narcosis is of significance in an evaluation of the relationship between degree of impairment and complexity of the task. Several authors have demonstrated this relationship in other than nitrogen stress situations. McFarland (15,16), in discussing the mental deterioration that occurs under hypoxia, states "on the whole the mental tests involving complex reactions showed the greatest relative loss in time and quality of response at the high altitudes, the motor tests second, and the sensory tests were least affected of all". The observation of differential impairment of psychological functions under conditions of hypoxia, anesthesia, sleep deprivation and other stresses has a long and varied history. The rationale for a hierarchical scheme of behavior organization is based upon the hypothesis that the more recent phylogenetic additions to the nervous system mediate the more complex forms of behavior and are depressed earlier and to a greater extent than the older and more primitive structures. Thus, performance on a complex reasoning task would be expected to show a greater impairment than simple psychomotor activity. Steinberg (24) offers an excellent review of this concept in her studies of the influence of depressant drugs on behavior. On the other hand there is some speculation to indicate that the higher functions are maintained long after one can note delayed reaction time, or latency of response and other measures of the less complex functions. Although there is some experimental evidence concerning a hierarchy of deterioration due to stress it is not conclusive. In addition, no investigation of this sort has been undertaken using nitrogen narcosis as the condition of stress.

1.3.2 An obvious application is the establishment of a single sensitive index of narcosis. With such a tool predictions could be made as to the performance of a diver on air at any depth-time relation. Application to HeO_2 and mix-gas diving would revolve around the relationship between appropriate gas mixture and task assignment. In addition, behavioral data would also be applicable to specifications for any self-contained environmental system which maintains an atmosphere at other than sea level conditions.

1.4 Objective

1.4.1 Considerable research data are available concerning physiological reactions under nitrogen narcosis. However, there is little research concerning the influence of this narcosis on physical performance and intellectual functions. Performance measures which have been utilized for the most part cannot be generalized above the rote memory level. In addition, objective studies of high thought processes and their relation to other performance under nitrogen stress are sparse. With the increase in activity of the Scuba unit and greater variability of the tasks assigned the underwater swimmer, it is essential that we know human performance tolerances.

1.4.2 Specifically, the primary goals of the present research are: (1) to determine whether performance decrement appears at a simulated depth of 100 feet; (2) to evaluate the relationship between the amount of decrement and the complexity of the task; (3) to investigate performance efficiency as a function of duration of exposure at a constant pressure.

2. EXPERIMENTAL DESIGN

2.1 Subjects

2.1.1 Ten subjects were used in the experiment; 2 senior medical students and 8 experienced divers including 1 medical officer. These men were picked in an effort to extend the range of variables of age, position and performance ability.

2.2 Tasks

2.2.1 Choice Reaction Time. The reaction time experiment has a long history which dates back to 1796 and is reported completely in Boring (5) and Murphy (20). The reaction time involved in this project is response to visual stimulation, colored light. The subject was seated before a panel on which were two lights, a red to the left and a green to the right. In each hand was held a switch which would extinguish the stimulus light on that particular side. The light stimuli were presented without prior warning at random intervals varying from 3 to 13 seconds. The subject's task was to continuously monitor the display panel and to respond as rapidly as possible to the appearance of a signal. Performance was measured in terms of reaction time in milliseconds. An experimenters view of the apparatus is shown in Figure II of Appendix B, while the subject's view is seen in Figure III of Appendix B.

2.2.2 Mechanical Dexterity Test. A modified Purdue Pegboard served as the measure of mechanical dexterity (6). The Pegboard, developed in 1941 by the Purdue Research Foundation, is the evolution of the development of Glenquist's first mechanical aptitude tests (25). The Pegboard itself is equipped with pins, collars, and washers all located in cups. The subject was required to place a small metal pin in the pegboard receptacle. He was then to place a small washer over the pin, a metal collar over the washer, and another washer over the collar. Performance was measured in terms of the number of parts assembled in thirty second periods. The pegboard is illustrated in Figure IV of Appendix B.

2.2.3 Conceptual Reasoning Test (CRT). This test, developed at the U. S. Naval School of Aviation Medicine for the purpose of evaluating reasoning ability under conditions of hypoxia, has been described in full elsewhere (13,14). In brief, the Conceptual Reasoning Test (CRT) consists of 32 small wooden blocks which embody the five dichotomous characteristics of : large-small, tall-short, round-square, hollow-solid, and numbered-lettered. Half of the blocks are similar in at least one characteristic. Eight of the blocks are similar in at least two characteristics; e.g., tall-hollow or square-short. Four of the blocks are similar in at least three characteristics; e.g., short-solid-small. None of the blocks are identical. Utilizing any one or all five dichotomous characteristics, one may classify the blocks in any of several different ways. It was the task of the subjects to determine the system of classification utilized by the experimenter. It will be recalled that any 8 of the 32 blocks may be classified by two of the characteristics, and the experimenter may use any one of the 8 blocks as a model which he places before the subject. It is the task of the subject to determine, by testing consecutive hypotheses which are confirmed or rejected by the experimenter, the remaining 7 having

the desired pair of characteristics in common with the model. Since the model embodies 5 characteristics, the only information provided the subject is that the correct solution must involve some paired combination of the 5 characteristics. Once the subject has been trained in the logical procedure for establishing and testing hypotheses to determine the correct pair, he reaches a relatively constant level of performance in terms of time and errors. Since the correct combination is changed with each problem presented, the test may be used repeatedly with the same subject. For purposes of the present study duel classification problems were used which involved only one-half (16) of the blocks. Problems were presented in sequence over four minute periods and performance measured in terms of time per problem. Errors were not measured since it became evident after the initial training that errors would be relatively infrequent. The CRT is shown in Figure V of Appendix B.

2.3 Task Discussion

2.3.1 One cannot speculate on the complexity of neural organization or phylogenetic level required for efficient performance on these 3 tasks. However, on an 'a priori' basis, the Purdue Pegboard test involving primarily finger dexterity and motor coordination would seem to be the least difficult. The Choice Reaction Time test, which presented stimulus signals in a random fashion without prior warning is in essence a vigilance test and required continuous attention and alertness as well as sensory-motor reception and response. The CRT, which includes the behavior required in the other 2 tests and also reasoning, judgement, and immediate memory, would be expected to be the most difficult and to portray a greater decrement in efficiency of performance under stress.

3. PROCEDURE

3.1 Pre-testing Procedure

3.1.1 Prior to the experimental sessions subjects were trained on all 3 tasks. Training continued until a constant level of efficiency was demonstrated through chance mean fluctuation of performance in successive training periods. It was assumed that these men trained to plateau level of performance were not affected by learning or memory carry-over and accurate measurements of decrement could be made.

3.2 General

3.2.1 During the experiment proper each subject was tested individually in a high pressure chamber. All dives were made dry, the respirable atmosphere at depth was compressed air. The rate of descent for each dive was 75 feet per minute. Rate of ascent from the bottom was 60 feet per minute. These rates were adhered to as strictly and as uniformly as possible. In addition, an effort was made to maintain similar conditions between the surface and 100 feet runs within acceptable tolerance limits. Temperature was controlled by air-conditioning, pressure by visual observation adjustment.

3.2.2 Each experimental session consisted of three phases; a measure of performance of all three tests at sea level pressure in the chamber; three 12 minute sessions at a pressure equivalent to a depth of 100 feet of sea water, during which time equal periods were allocated to performance measurements in each of the three tasks; a final measure obtained during a period of decompression at a depth of 10 feet. Data were recorded during the final period of decompression merely to indicate that, if impaired performance was demonstrated, it was a function of nitrogen narcosis and not simply work decrement resulting from fatigue. That is, if performance is impaired due to the increased partial pressures of nitrogen at 100 feet, one would expect a return to approximately normal performance efficiency during the period of decompression.

4. RESULTS AND DISCUSSION

4.1 Performance Decrement at 100 Feet

4.1.1 As indicated in Table 1, all subjects demonstrated performance decrement between sea level pressure and 100 feet of pressure on all three tests. All subjects demonstrated a return to approximately normal performance during the 10 foot decompression stop on the three tasks. The group decrement in performance occurring during the period of measurement is shown to be above chance expectancy at better than the .01 level of confidence (Table 2).

TABLE 1

SUMMARY OF MEANS TEST PERFORMANCE AT TWO PRESSURE CONDITIONS

Subjects		Reaction Time (1/100 Seconds) S	Reaction Time (1/100 Seconds) 100 ft.	Mechanical Dexterity (Pieces Assembled) S	Mechanical Dexterity (Pieces Assembled) 100 ft.	Conceptual Reasoning (Seconds) S	Conceptual Reasoning (Seconds) 100 ft.
	M	25.1	31.5	22.4	21.5	9.3	11.5
1	SD	4.3	8.5	1.4	1.8	2.0	2.3
	M	26.1	27.8	28.5	26.7	8.3	9.7
2	SD	4.6	2.5	2.1	1.4	2.2	2.3
	M	26.2	30.2	26.3	25.4	8.0	10.9
3	SD	5.1	6.1	1.0	1.6	1.2	2.9
	M	25.9	31.8	32.3	28.1	7.6	11.0
4	SD	4.3	5.2	0.9	1.1	2.2	2.5
	M	25.0	33.9	24.8	19.8	7.6	12.2
5	SD	4.0	6.5	1.6	1.3	1.2	2.9
	M	23.7	26.8	29.0	26.2	6.5	8.0
6	SD	3.6	4.9	2.4	1.2	1.7	1.6
	M	22.7	25.4	26.0	25.3	8.9	10.2
7	SD	5.7	6.1	1.4	1.6	2.4	2.8
	M	23.8	27.4	29.6	27.1	7.4	11.8
8	SD	3.3	4.8	1.9	2.5	2.0	2.6
	M	23.8	26.3	30.3	29.8	6.7	8.3
9	SD	4.5	4.4	1.0	1.6	1.4	2.4
	M	20.3	24.1	30.8	27.5	6.4	8.2
10	SD	4.1	3.9	2.2	1.3	1.4	2.1

TABLE I

TABLE 2

t TESTS OF CORRELATED MEANS BETWEEN TEST PERFORMANCE AT SEA LEVEL AND 100 FEET

		Sea Level	100 Ft.	SE_{dm}	t
Reaction time	M	23.74	28.69	0.728	6.800*
(1/100 seconds)	SD	4.86	6.38		
Mechanical Dexterity	M	28.09	25.87	0.500	4.440*
(Pieces assembled)	SD	2.84	2.07		
Conceptual reasoning	M	7.68	10.25	0.468	5.491*
(Seconds per problem)	SD	2.07	2.82		

* Significant at greater than .01 level.

TABLE 2

4.1.2 In terms of the initial goal of the experiment these findings are of significance. Previous research in this area has been primarily undertaken at pressure levels exceeding 200 feet. In fact, statements exist in the literature to the effect that nitrogen narcosis does not appear until depths of 150-200 feet are exceeded (18). A demonstration of impaired performance at the 100 foot depth indicates that the relationship between task assignment and performance efficiency be given serious consideration even at relatively low levels of nitrogen partial pressure.

4.2 Task Complexity vs. Degree of Impairment

4.2.1 The second aim of the experiment was to investigate the relationship between task complexity and loss in performance efficiency. Tables 3 and 4 show that the degree of decrement increases with increase in complexity of the task and that these differences exceed chance expectancy at better than the .01 level (17).

4.2.2 Since there is overlap in the behavior required for the execution of the three tasks one cannot accept without qualification a hypothesis concerning the relationship between performance impairment under the stress of nitrogen narcosis and levels of neural organization. However, to the extent

that complexity of behavior is correlated with the complexity of the neural pathways, evidence is presented which indicates that the neural structures which support reasoning and immediate memory show greater functional impairment than do those supporting simple motor coordination and choice reactions. Aside from these speculations a demonstrated difference in performance efficiency between various tasks helps to account for contradictions in other research investigations which indicate little or no performance decrement at depths exceeding 150 to 200 feet. The presence or absence of impaired performance appears to be largely a function of the performance measure one uses. These findings are also relevant to the assignment of job requirements in a vehicle or other system which utilizes increased atmospheric pressure. If the individual merely has to perform a simple manual task the pressure level may be quite high without severe impairment. However, if he is required to determine decompression schedules, or perform other complex intellectual activity as in explosive ordnance disposal, the effect of the breathing medium must be relatively close to that of air at sea level.

TABLE 3

PERCENT DECREMENT IN PERFORMANCE BETWEEN SEA LEVEL AND 100 FEET FOR EACH OF 3 TESTS

	Percent Decrement
Reaction Time	20.85
Mechanical Dexterity	7.90
Conceptual Reasoning	33.46

TABLE 4

't' TESTS OF PERCENT DECREMENT AT 100 FEET BETWEEN THE THREE TASKS.

TESTS	σ Dp	p.01	't' (CR)
CRT vs. MDT	3.50	2.588	4.45*
CRT vs. RT	3.04	2.576	4.18*
MDT vs. RT	2.58	2.576	5.00*

*Significant at the p.01 level of confidence.

TABLES 3 AND 4

4.3 Performance Efficiency as a Function of Time

4.3.1 The third question concerned performance efficiency as a function of duration of exposure. Results are shown in Figure I. It may be noted that performance remains impaired but relatively constant after the initial decrement under pressure and then improves again during the period of decompression. Chance differences were shown to exist between the three measurements taken under pressure for each of the tests.

4.3.2 This finding indicates the relationship existing between overt behavior and the physiological mechanisms underlying the behavior. As the subject is exposed to increased pressure there is a period of physiochemical adjustment as nitrogen saturation is increased. After an interim of time, the saturation level reaches a steady state which is reflected in impaired but constant performance. The finding that decrement in performance appears during the initial 12 minute period at a depth of 100 feet would lead one to question Alpha Blocking and CFF as sensitive indices of nitrogen narcosis.

FIGURE I

MEAN PERCENT DECREMENT FOR COMBINED TESTS
AS A FUNCTION OF DURATION OF EXPOSURE

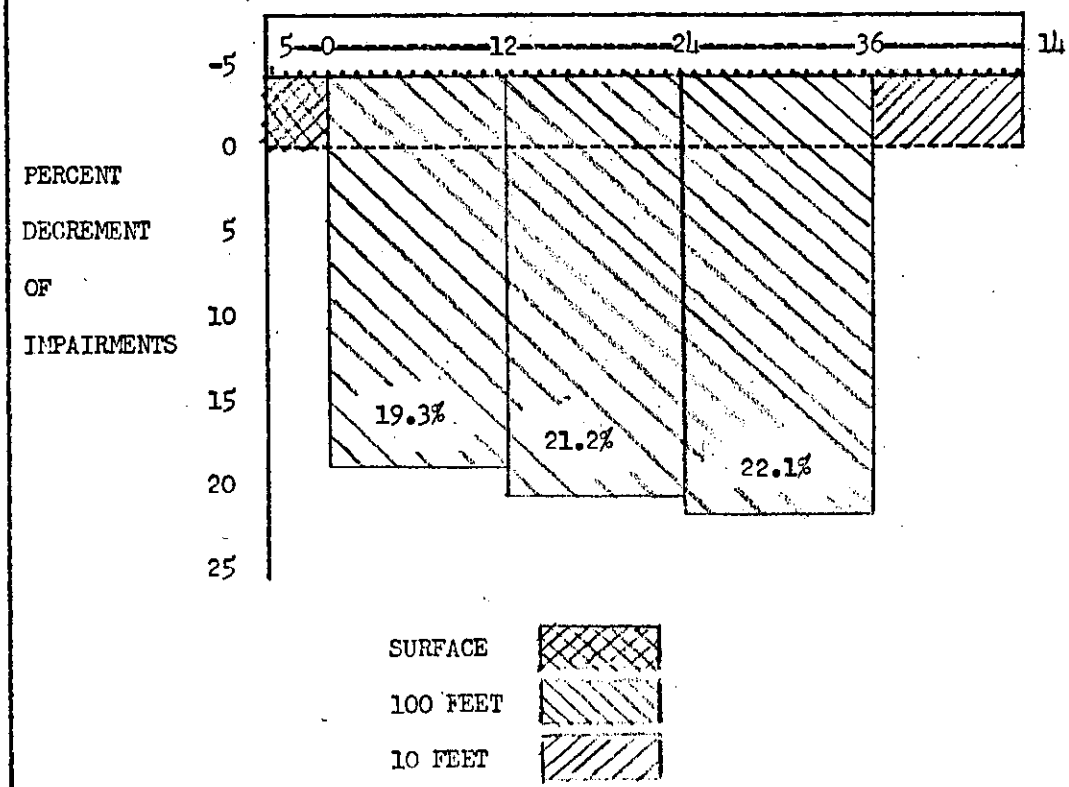

FIGURE I

5. CONCLUSIONS

5.1 In terms of practical significance the present experiment indicates that performance decrement occurs at depths as shallow as 100 feet. When compared with their individual sea level efficiency all of the subjects demonstrated significant decreases in performance on all the tests.

5.2 The findings that the amount of decrement is a function of the complexity of the task is theoretical in nature. A definite position relationship exists between task complexity and performance with reasoning ability showing the greatest decrement, choice reaction time less, and motor dexterity the least.

5.3 Finally, the time of exposure was not related to the degree of performance impairment. There is an initial loss in efficiency as pressure is increased and this level of impairment remains relatively constant with increased duration of exposure.

6. RECOMMENDATIONS

6.1 It is recommended that current experimentation be directed toward: a determination of relative impairment at varied depths; an evaluation of continuous performance of a single task at constant depths; and the amount of individual and group variability to be expected as a function of depth and duration of exposure.

6.2 If those recommendations provide an adequate quantitative measuring instrument, it is recommended that comparative evaluations of performance decrement and variables as extended practice, drug administration, changes in breathing rhythm, and exercise be investigated. The possibility of determining significants in respiratory response to CO_2 due to central respiratory 'center' narcosis also exists. These possibilities all are aimed at increasing the divers effectiveness and safety.

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APPENDIX A

GLOSSARY

CFF	Critical Flicker Fusion
CRT	Conceptual Reasoning Test
M	Arithmetic Mean
MDT	Mechanical Dexterity Test
p.01	Confidence level including 99/100 cases
RT	Choice Reaction Time
S	Surface, sea level
SD	Standard deviation — σ
SE_{dM}	Standard error of the difference between means
't' Test	Small sample statistics (Critical ratio)

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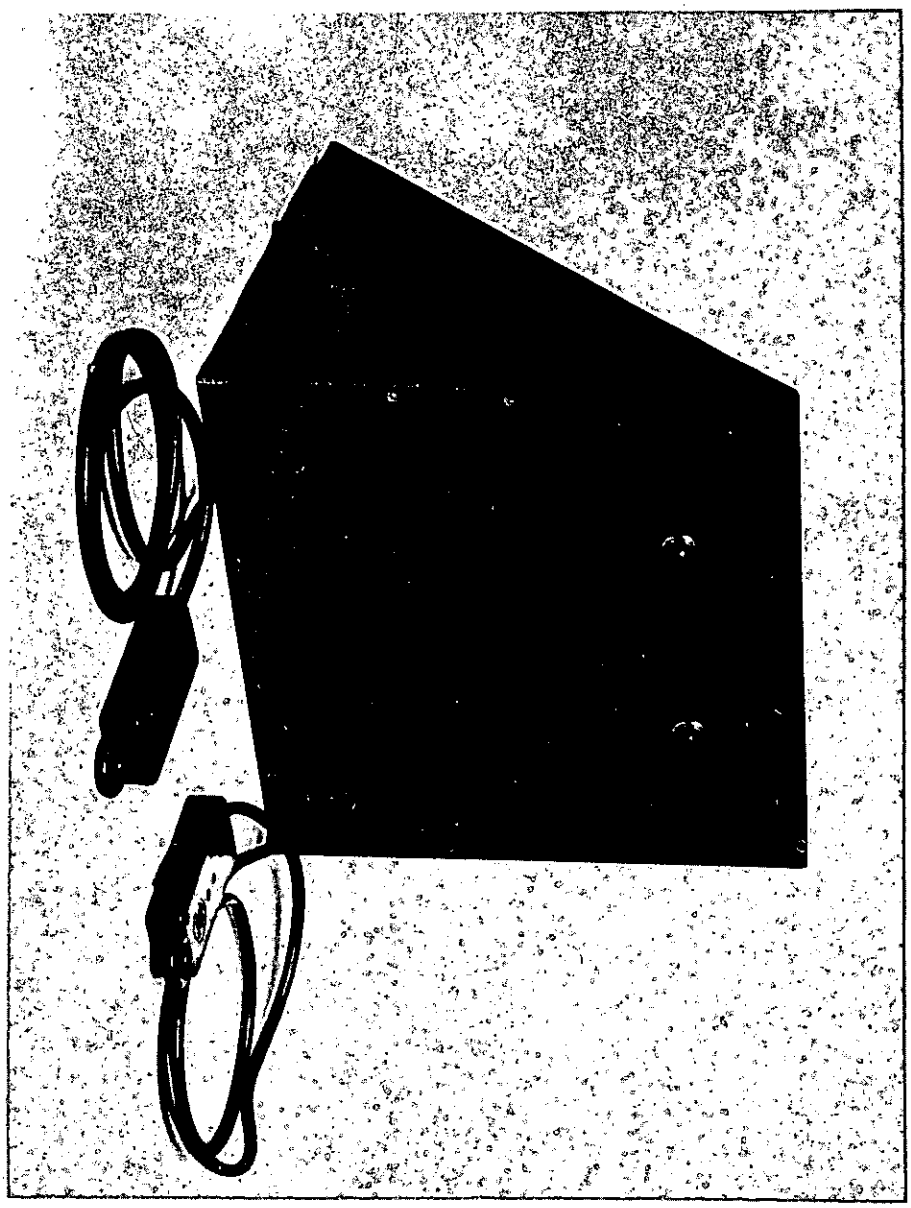
APPENDIX B - FIGURE II



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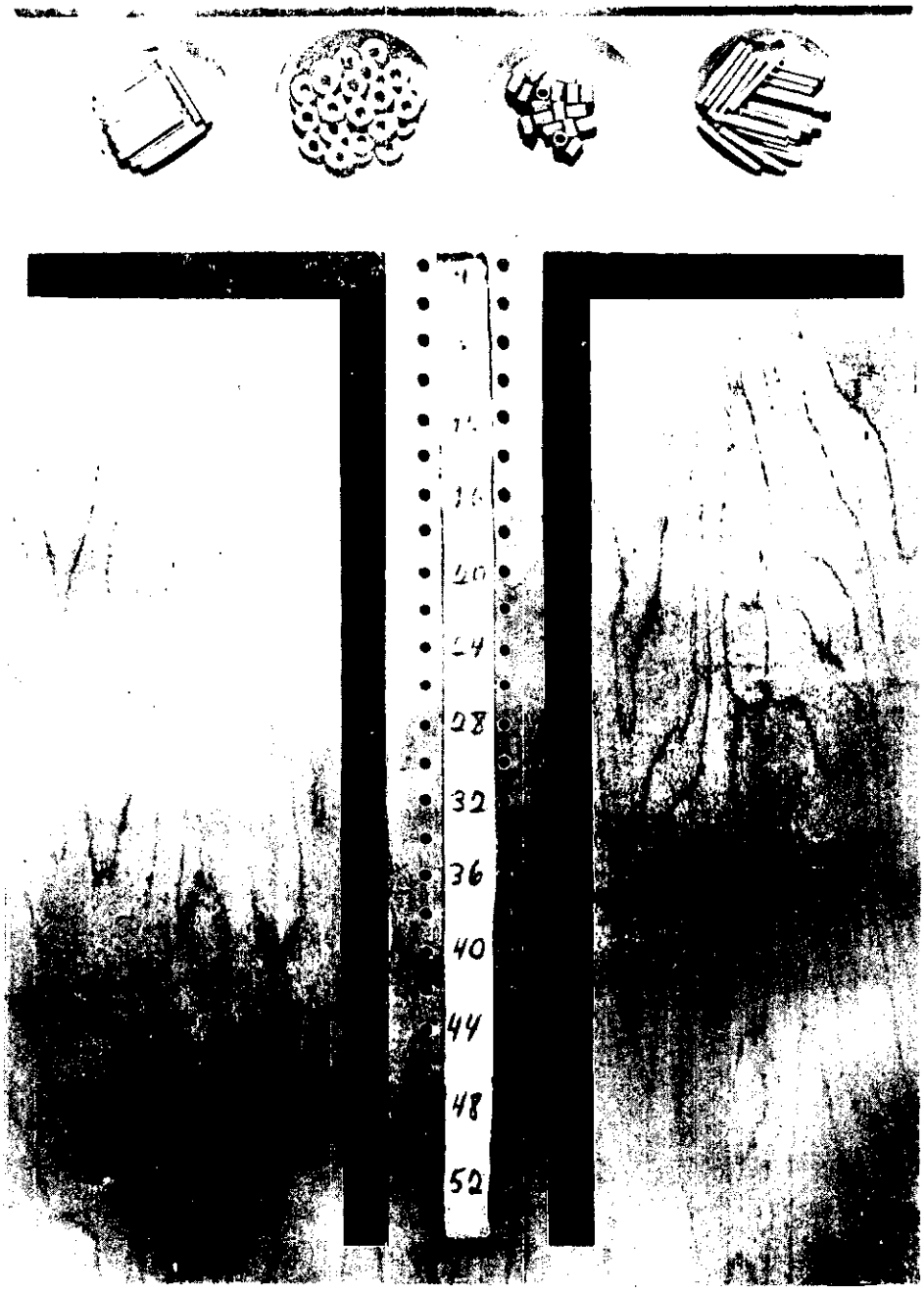
APPENDIX B - FIGURE III



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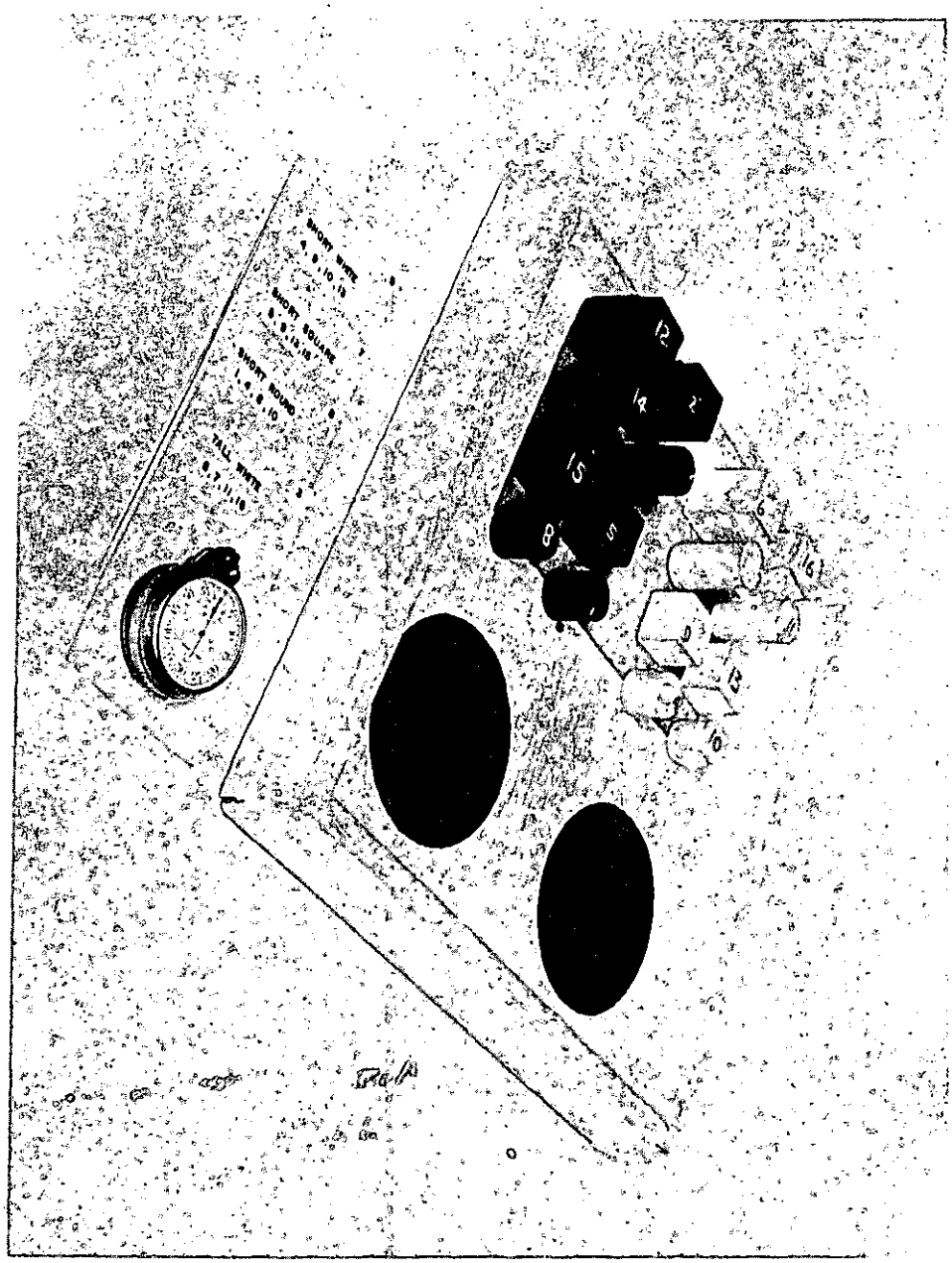
APPENDIX B - FIGURE IV



19 APPENDIX B - FIGURE V

(Reprinted from Nature, Vol. 231, No. 5302, pp. 368–371, June 11, 1971)

Pressure Reversal of Anaesthesia

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The application of high hydrostatic pressure will remove, at least partially, the effects of general anaesthetics in both newts and mice. This feature seems to be common to all general anaesthetics and a simple model could explain this antagonism.

THE first observation of the effects of hydrostatic pressure in modifying the response of organisms to drugs is due to Johnson and Flagler[1]. Having observed that the application of pressure could restore the luminosity of luminous bacteria that had been exposed to an anaesthetic agent, they tried a similar experiment on tadpoles narcotized with ethyl alcohol. The effect of 2–5% alcohol is to narcotize the animals so that they cannot swim and fall to the bottom of the vessel. In the absence of the alcohol the tadpoles responded to pressure by increased activity at 130 atmospheres and exhibited paralysis at about 300 atmospheres. If a pressure of 200–300 atmospheres is applied to the anaesthetized tadpoles they resume swimming in an apparently normal manner. Similar results are reported here for newts and mice using the narcotic or anaesthetic gases N_2 and SF_6, a barbiturate anaesthetic and two common clinical anaesthetics, ether and halothane.

The effects of high hydrostatic pressures alone on *living* organisms have been under active investigation for almost a century[2]. The classic work of Regnard[3] and subsequently Ebbecke, Cattell and others showed that the first effect of pressure on aquatic animals is to stimulate the central nervous system; this happens above 50 atmospheres[4]. At higher pressures (200–300 atmospheres) spontaneous muscle contraction occurs and the animals become paralysed. Still higher pressures (about 400 atmospheres) are lethal. In experiments with mammals, it is not always easy to distinguish between the effects of pressure as such and the narcotic effects of the gases breathed. Thus Italian newts lose their ability to right themselves at pressures between 165 and 245 atmospheres

whether the pressure is applied with helium or neon, or even hydrostatically[5]. Newts and mice have been shown to be similarly susceptible to anaesthesia by nitrogen, but mice exposed to high pressures of helium and neon are not anaesthetized even though both gases proved lethal at 135–145 atmospheres. This is the origin of the view that helium (and perhaps neon) have anaesthetic pressures for mice and newts greater than the tolerable mechanical pressures, and that these gases can be used to study the effects of pressure as such on mammals.

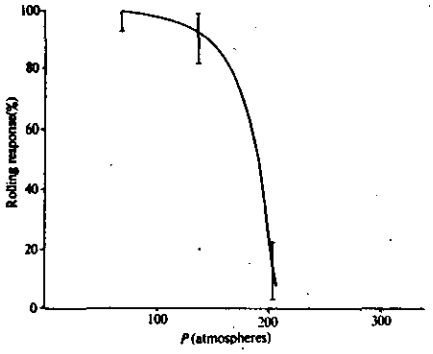

Fig. 1 Rolling response of newts as a function of hydrostatic pressure (in water). Error bars indicate the 95% confidence limits. Ten animals were used in the experiments. The temperature was 20° C, and the rotation speed was 4 r.p.m.

The results of experiments so far indicate that there are four principal effects of hydrostatic pressure on mice[6–8]. (i) Uncoordinated tremors (onset 70 ± 10 atmospheres) which may depend on the rate of compression; (ii) convulsions—which have been observed at somewhat higher pressure by most but not all investigators; (iii) respiratory distress at pressure above 90 atmospheres, and (iv) paralysis.

Experiments with Newts

To investigate the effects of pressure and anaesthetics we have carried out further studies on the Italian crested newt (*Triturus cristatus carnifex*), which can be exposed to hydrostatic pressure both directly (in water) and using a gas. It resembles the mouse in having a rapid righting reflex and it shows a similar sensitivity to anaesthesia in the presence of simple gases. The experiments were carried out in a high pressure cylindrical chamber of 0.3 l. volume fitted with a window at one end. The chamber could be rotated at four revolutions per minute and the ability of the animals to follow the revolutions (rolling response) observed. The animals which rolled over completely during any one revolution were ascribed a zero score; all others scored one. Sets of five revolutions were observed and a final performance recorded as a percentage score. Failure to respond could arise either from the effects of narcosis or from the impairment of movement produced by very high pressures above 140 atm. The experiments were carried out at 20° C and the partial pressure of oxygen was initially 1 atmosphere. This provided sufficient oxygen for mice to survive for 3 h. Newts proved considerably less sensitive to anoxia than mice; nevertheless observations were restricted to the first 90 min. A soda-lime canister which could be moved up and down the chamber was used to keep the partial pressure of CO_2 below 1.5 mm Hg.

The first series of experiments were carried out using hydrostatic pressure alone. The pressure vessel was filled with water and no free gases were present. As the pressure is raised occasional failure to follow the revolutions of the chamber is observed at 100 atmospheres and the failure is almost total at 200 atmospheres. Exposure to high pressures of helium and neon gave rise to similar responses although there is evidence that the onset of the adverse effects occurs at somewhat higher pressures than with hydrostatic pressure alone (Figs. 2 and 3).

To investigate the antagonism between pressure and anaesthetic agents a further series of experiments were carried out with newts that had been anaesthetized with 34 atmospheres of nitrogen. In this condition they were unable to respond to the rotation of the chamber. But when they were subjected to higher pressures by the addition of helium, this ability was almost completely restored at 140 atmospheres. Further increase in the pressure led to a subsequent decline in the rolling response, but even at almost 300 atmospheres the response was at the 50% level (Fig. 4).

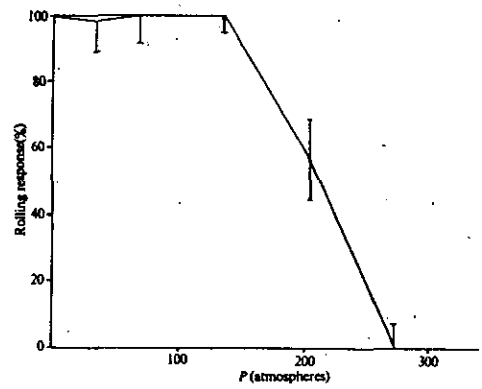

Fig. 2 Rolling response of newts as a function of helium pressure. The oxygen partial pressure was 1 atmosphere. Other conditions were as for Fig. 1.

To demonstrate that the narcosis is antagonized by pressure *per se* and not by some interaction specific to helium, experiments were performed in which the pressure was raised mechanically (no gas phase being present). Newts were totally immersed in sodium pentobarbitone solution (0.4 mg/ml.) in the pressure chamber. When the hydrostatic pressure was raised to 140 atmospheres the rolling response increased from 4% to 56%. Similar antagonism between anaesthesia and hydrostatic pressure has also been demonstrated in preliminary experiments on ether (32 mM), halothane (1.15 mM) and butanol (28 mM) in aqueous solution.

Experiments with Mice

The experiments were carried out in a 1.5 l. chamber capable of working to pressures of 300 atmospheres. The internal dimensions of the chamber which was closed with a Graylock seal were 20 cm by 10 cm. The interior could be observed through two 1 inch diameter toughened glass windows. Gas at pressures greater than those in the supply cylinders was obtained from a compressed air driven pressure intensifier. The mice were exposed in pairs in large mesh wire cages. A powerful fan driven by an induction motor ensures mixing of the gases (a serious problem at very high pressures) and CO_2 removal at the scrubbers. The initial partial pressure of oxygen was adjusted to 1 atmosphere and was not allowed to fall to less than 0.5 atmospheres during the experiments. The chamber was maintained at a temperature of 30° ± 3° C. In the case of mice the effects of high pressure are to some extent

dependent on the rate of compression. The pressures at which tremors and convulsions are first observed at compression rates varying by a factor of twenty are given in Table 1. Approximately half the deaths reported in Table 1 were associated with convulsions; the remainder either occurred suddenly or, especially at the higher pressures, after a moribund period. The cause of death when not associated with convulsions was not obvious. To investigate whether respiratory distress was a contributing factor a series of comparative tests with neon was carried out. The molecular weight, and thus the density at any given pressure, of neon is five times that of helium. Mouth breathing was observed above 95 atmospheres, but although respiratory distress was more marked than with helium the lethal threshold was not significantly different (Table 2). Furthermore, mice exposed to high pressures (20 atmospheres) of CF_4 (ref. 10) have survived in a gas density nearly three times that at which death occurs with helium. Even under slow compression, the pressure which proves lethal for mice produces only a 10–15% diminution in the ability of newts to follow the revolutions of the chamber (Table 3). The greater sensitivity of mice to high pressure could be due to their absolute dependence for life on rhythmic cardiac and respiratory muscular activity.

Table 1 Effect of Compression Rate

Compression rate (atm/min)	No. of mice	Threshold pressure (atmospheres) Tremor	Convulsion	Death
10	3	35–50	70–80	136±6
1.25	9	60–100	95–120	135±3
0.5	3	75–109	105–120	159±4

Inert gas: helium. Po_2: 0.5–1.0 atmospheres. Temperature: 30°± 3° C.

Table 2 Experiments with Mice at Very High Pressures

Inert gas	No. of mice	Threshold pressure (atmospheres)±s.d. Tremor	Convulsion	Death
He	9	74±8	108±4	135±3
Ne	6	88±3	130±7	144±11
With anaesthetic He+45 atm N_2	4	—	—	166±3
He + barbiturate*	4	—	—	200±6

Po_2: 0.5–1.0 atmospheres. Temperature: 30°±3° C.
Average compression rate: 1.25 atmospheres/min.
* 0.1 mg/g Na pentobarbitone.

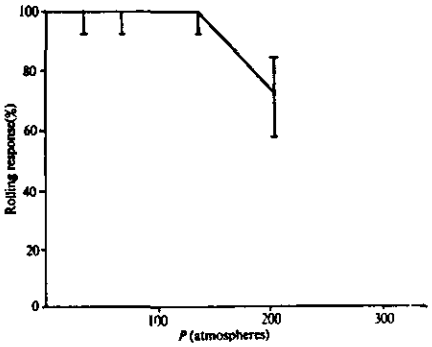

Fig. 3 Rolling response of newts as a function of neon pressure. The oxygen partial pressure was 1 atmosphere. Other conditions were as for Fig. 1.

In spite of these effects of pressure the reversal of anaesthesia was observed in mice. Thus when mice anaesthetized with 45 atmospheres of nitrogen were subjected to further compression with helium the anaesthesia was reversed and the animals exhibited spontaneous activity again just as in the case of newts. Similar success was obtained with mice anaesthetized with sodium pentobarbitone (0.1 mg/g subcutaneously). Furthermore, in these conditions tremors and convulsions were less distinct and both agents produced a significant increase in the lethal pressure (Table 2).

Site of Anaesthetic Action

Recent studies[9–11] have tended to point to hydrophobic regions within the body as the site of action of anaesthetics and have lent little support to the "hydrate" theories of Pauling[12] and Miller[13]. The results are consistent with the lipid solubility model which supposes that anaesthesia occurs when a chemically indifferent substance attains a critical concentration in the cellular lipids[14]. This concept may be extended to account for the effects of pressure and temperature. It is proposed, following many earlier workers[15], that the important action of anaesthetic molecules is to modify the dimensions of lipid regions, possibly those in cellular membranes. Anaesthetic potency would then be proportional to the product of the solubility of the agent in lipids and its partial molar volume. (It has not proved possible to distinguish this model from one in which potency is simply proportional to fat solubility using available experimental data since molar volumes vary over too narrow a range compared with the variation of solubility.) The site of action of anaesthetics corresponds to a region of solubility parameter $\delta = 9 \pm 1$ (calories $cm^{-3})^{\frac{1}{2}}$ where

$$\delta = \left(\frac{-E^{vap}}{V}\right)^{\frac{1}{2}}$$

and E^{vap} is the energy of vaporization and V the molar volume of the solvent region[9,10]. This value of the solvent power can be used to estimate other physical properties of the region. Thus for a van der Waals fluid

$$\delta^2 = \left(\frac{\partial E}{\partial V}\right)_T = T\left(\frac{\partial P}{\partial T}\right)_V = T\frac{\alpha}{\beta}$$

where α is the coefficient of thermal expansion and β the coefficient of isothermal compressibility. For a solvent for which $\delta = 9$ (calories $cm^{-3})^{\frac{1}{2}}$, changing units gives $\delta^2 = 3{,}320$ atmospheres; then

$$\left(\frac{\partial P}{\partial T}\right)_V = \alpha/\beta = 11 \text{ atmospheres deg}^{-1}$$

that is, an 11 atmosphere rise in pressure at the temperature concerned, would be required to nullify the expansion caused by a 1° C temperature rise. Assuming a reasonable value for α of, say, $\sim 0.5 \times 10^{-3}$ deg^{-1} would lead to an estimate for β of $\sim 5 \times 10^{-5}$ $atmosphere^{-1}$. (For benzene at 25° $\alpha = 1.2 \times 10^{-3}$ deg^{-1} and $\beta = 9 \times 10^{-5}$ $atmosphere^{-1}$; for olive oil at 15° C $\alpha = 0.7 \times 10^{-3}$ deg^{-1} and $\beta = 6 \times 10^{-5}$ $atmosphere^{-1}$ (refs. 16, 17).) The critical anaesthetic concentration in the lipids can be estimated to be ~0.05 M[18], and because the partial molar volumes[20]

of anaesthetics are in the range 50–100 cm³ an anaesthetic dose would produce an expansion of lipids of the order of 0.4%. Using the estimated value of β the pressure increase required to nullify this expansion can now be calculated to be of the order of 100 atmospheres. This is consistent with the pressures experimentally required to remove the effects of a normal anaesthetic dose. *It follows from the model that the pressure* required should be directly proportional to the partial molar volume of the anaesthetic agent and the dose used. The results of preliminary experiments suggest that these consequences of the model can be seen. Thus if newts are anaesthetized with 68 atmospheres of nitrogen (twice the anaesthetic dose used in the experiment described earlier) the recovery of the rolling response at 140 atmospheres total pressure (N_2 + He) is only about 50%. Similarly, preliminary experiments show that 140 atmospheres pressure only produces a 50% recovery in newts exposed to a normal anaesthetic dose of SF_6 (ref. 19) (estimated molar volume 76 ml. whereas that of nitrogen is 35 ml. (ref. 15); the partial molar volumes in benzene ($\delta = 9.2$) are 97 ml. and 53 ml. respectively[20]). An interesting prediction can be made that hydrogen would be the most successful gas to use at high pressures, the expansion due to its solution being almost exactly balanced by the compression due to pressure.

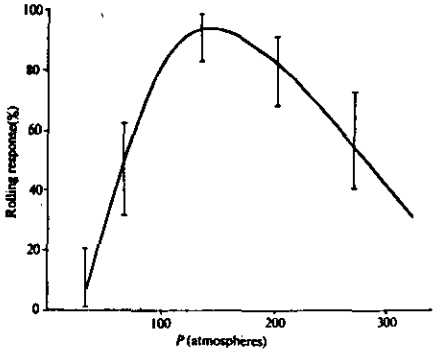

Fig. 4 Rolling response of newts as a function of helium pressure in the presence of 34 atmospheres nitrogen. The oxygen partial pressure was 1 atmosphere. Other conditions were as for Fig. 1.

It is a further consequence of the model that cooling by ~10° C should antagonize the effects of normal doses of anaesthetics. With whole animals the predominant effect of lowering the ambient temperature is hypothermia (which results in loss of activity in goldfish at 2° C) (ref. 21). Where higher doses of anaesthetics are required at low temperatures the explanation most readily given is in terms of changing solubility relations[22]. But Spyropoulos[23] showed that the reduction in the action potential in a toad single nerve fibre induced by application of a 3% ethanol solution could be removed by cooling by 15° C or by applying 500 atmospheres

Table 3 Comparison of Mice and Newts

	Lethal limit for mice (atm)	% RR of newt at this pressure
He	159	85
Ne	(159)	90
He–N_2	166	92

pressure. The reversal of anaesthesia by pressure in luminous bacteria *has already been noted. A further feature of the* bacterial system which is in keeping with the simple model we propose is that if the bacteria are above their optimum temperature for luminescence the application of hydrostatic pressure will increase the level of luminescence[24].

It is not possible to define precisely where the lipid region involved in anaesthesia is located but two areas could be important. First, hydrophobic areas within certain specific enzymes have been proposed as the site of action of anaesthetics, for example such an area has been invoked to explain the action of competitive inhibitors on α-chymotrypsin[25]. Furthermore, the response of luminous bacteria to anaesthetics and the antagonism of this response by high pressures has been interpreted in terms of the effects of these agents on the enzyme responsible for the luminescence, luciferase. No enzyme sufficiently sensitive to anaesthetics has yet been identified in the central nervous system however. Second, there are the lipids of the cell membrane where various actions could take place. Distortion or disordering induced by the anaesthetic could reduce control of or alter permeability; some workers have suggested that anaesthesia results from increased permeability[26,27], and others that it results from decreased membrane permeability[28]. It is possible that the disturbance of the lipid part of the membrane is transmitted to some functionally vital protein in such a way as to render it inoperative.

This research was supported in part by the US Office of Naval Research.

Received November 20, 1970; revised March 22, 1971.

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Printed in Great Britain by Flarepath Printers Limited, Colney Street, St. Albans, Herts.

ACSIL/ADM/60/144

A.C.S.I.L. TRANSLATION NO. 1086

THEORY OF NARCOSIS BY INHALLATION ANAESTHESIA

K. H. Meyer and H. Gottlieb-Billroth

Zeitschrift für physiol. Chemie,

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(From German)

DEPARTMENT OF RESEARCH AND DEVELOPMENT SERVICES

ADMIRALTY

April, 1960

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According to the theory propounded by Hans Horst Meyer [1]* and shortly afterwards, independently, by Overton [2], narcosis is the result of the change in the normal state of a cell caused by inert narcotics being dissolved in the cell lipoids. This theory, known as the "lipoid theory of narcosis" was summarized by H. Meyer in the following principles:

1. All substances which, chemically, are mainly inert and which are soluble in fat and fatty substances must have a narcotic action on living protoplasm so far as they are able to propagate themselves in it.

2. The effect will inevitably appear first and strongest in the cells having a predominance of these fatty substances in their chemical composition and which are most probably important carriers of the cell functions; thus the nerve cells in particular.

3. The relative effectiveness of these narcotics must be dependent on the one hand on their mechanical affinity to fatty substances and on the other hand to the remaining body constituents, i.e. mainly water, consequently on the distribution coefficient which determines their distribution in a mixture of water and fatty substances.

Both H. Meyer and Overton verified the quantitative relation mentioned in the last sentence, using aquatic animals 9tadpoles) for their experiments. They determined, for a very wide variety of substances, not only the concentrations which had a narcotic effect but also the distribution coefficients between olive oil - which was chosen as the lipoid - and water. The narcotic effectivenesses - expressed by the reciprocal values of the limit concentrations - and the distribution coefficients oil/water ran parallel.

Now, if narcotics are used, not in aqueous solution but as gaseous anaesthetics for inhalation, a distribution within the organism according to the distribution coefficient can still be expected; but the relation between effectiveness and solubility in the lipoid, to be expected according to Meyer and Overton, does not include the distribution coefficient lipoid water, as will be shown in the following consideration.

According to Paul Bert [3], in order to bring about and maintain narcosis it is necessary in the case of each anaesthetic that the inhaled air shall contain a definite fraction (part by volume) of narcotic (at 760 mm). The "effectiveness" can therefore be defined logically as the reciprocal value of this fraction. The quantity of narcotic

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*For references, see end.

dissolved in the lipoids when narcosis occurs - which is the critical factor according to the lipoid theory - depends now upon the coefficient of solubility of the gas in the lipoid*. In this connection, as Overton in particular has emphasised, it is immaterial in what way the equilibrium distribution of the narcotic between the gas volume and the lipoid, which finally occurs with the limit concentration for narcosis, is achieved; whether directly or through the agency of plasma. Even though the plasma must naturally possess a certain minimum capacity for dissolving the anaesthetic, so that it does not form a dividing wall between the lipoid and the volume of gas, nevertheless the magnitude of this dissolving capacity is of no importance as regards the lipoid/gas volume equilibrium position.

According to this, therefore, if the lipoid theory is correct, there is a close connection to be expected between the effectiveness and the solubility coefficient in the lipoid when gaseous narcosis is employed.

This inference which has been drawn from the lipoid theory is verified experimentally below.

CHOICE OF NARCOTICS

In many works dealing with narcosis the comparison is made chiefly between homologous substances of the same series, whose effectiveness, as Richardson [4] has already discovered, increases uniformly with the number of carbon atoms. In our opinion, however, experiments which arrive at a state of parallelism between the effective strength and another property constitute no proof at all of any original connection between the two if the substances under experiment are substantially only those of homologous series. The so-called "Law of homologous series" of Richardson can have no decisive significance for any theory of narcosis. This is because all the physical and chemical properties, such as melting point, boiling point, molecular volume, heat of combustion, solubility, distribution coefficient, surface action, viscosity, adsorbability, catalytic or anti-catalytic effect (on enzymes also), dissociation constant in the case of acids, rate of saponification in the case of esters, change within homologous series with increase of carbon atoms at regular intervals, so that it is possible to build up from them the connections between narcotic effectiveness and each of these properties. We think that inferences about such a connection are only justified where there exists behaviour in the same direction, or still better proportionality, in members of many different classes.

We therefore investigated inert gaseous or easily vaporisable substances from 9 different series: nitrous oxide, diethyl and dimethyl ether, amylene, ethylene oxide, several acetals, ethyl chloride and methyl chloride, methyl bromide and ethyl bromide, dichlorethylene, chloroform.

METHOD, WITH LIMITS OF ERROR AND FINDINGS

We determined the content of narcotic in the air, by volume, (related to air at 760 mm pressure) which caused mice to fall into just a light narcosis after $\frac{1}{2}$ — $\frac{3}{4}$ hour. If they are not narcotised by then

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*L = solubility coefficient (Nernst) = solubility according to Ostwald = number of volumes of gas which absorbs one part by volume of a liquid absorbent. Synonymous with distribution coefficient $\frac{\text{absorbent}}{\text{volume of gas}}$.

they generally continue in an awake state, while if they are just narcotised they wake up again if there is a slight reduction in the amount of anaesthetic in the air. This shows that equilibrium has been established in the distribution between the volume of gas and the organs whose function is under observation. It is of no significance whether there is subsequently a flow of narcotic into remote organs, e.g. adipose tissue, with consequent increase for some time in the amount of narcotic in the arterial blood over that in the venous blood.

The concentrations of narcotic which are just effective can be determined with an accuracy of about ± 20% on animal material which is as uniform as possible.

We also determined the coefficients of solubility of the vaporised narcotics in vegetable oil (olive oil or sesame oil).

Undoubtedly the correct procedure would be to determine the coefficients of solubility in the brain lipoids themselves. It is not possible, however, to study the brain lipoids free from water, albumins, etc., in the same physical state as that in which they are present in the organism, viz. in the emulsoid state which is closely related to liquids. The lipoid mixture which is obtained by the pulverisation of brain with dry sodium sulphate, extraction with chloroform and drying in an absolute vacuum is a brittle mass, with a high melting point, which in an atmosphere containing ether or chloroform increases in weight slowly, for weeks. We were therefore compelled to make use of a liquid fat.

According to our observations on oil, Henry's law applies for low partial pressures such as are met with in narcosis in the case of gaseous substances and those boiling at low temperatures. With substances boiling at higher temperatures, deviations appear, in that the coefficient of solubility increases with rising pressure. The solubility coefficient given in the Table is that appropriate to the partial pressure which produces a narcotic effect.

The results, with the limits of error, are summarised in the following Table.

Substance	C = narcotic concentration in Vol.%	W = effective strength = 100/C	L = solubility coefficient at 37°	C_{Lip} = concentration of narcotic in lipoid in Mol/litre.
Nitrous oxide	100	1	1.40±0.1	0.06 ± 0.01
Dimethyl ether	12 ± 2	8.3	11.6 ±0.1	0.06 ± 0.01
Methyl chloride	6.5 ± 1.5	15.4	14.0 ±1	0.04 ± 0.01
Ethylene oxide	5.8 ± 1.8	17.3	31 ±4	0.07 ± 0.03
Ethyl chloride	5.0 ± 0.8	20	40.5 ±1	0.08 ± 0.02
Methyl bromide	> 2.3, ca.3-4	25-30	32 ±1.5	ca.0.04
Amylene	4.0 ± 0.5	25	65 ±6	0.10 ± 0.03
Diethyl ether	3.4 ± 0.3	29	50 ±4	0.07 ± 0.01
Methylal	2.8 ± 0.4	35	75 ±6	0.08 ± 0.02
Ethyl bromide	1.9 ± 0.3	53	95 ±4	0.07 ± 0.01
Dimethylacetal	1.9 ± 0.3	53	100 ±10	0.06 ± 0.02
Diethylformal	1.0 ± 0.2	100	120 ±10	0.05 ± 0.01
1.2-ethylene-bichloride	0.95 ± 0.1	105	180 ±10	0.05 ± 0.01
Chloroform	0.44 ± 0.04	228	265 ±7	0.05 ± 0.01
				Average: 0.06

It will be seen that the effective strength and the solubility coefficient do not only move in the same direction, but are approximately proportional.

We can now calculate from the solubility coefficients the molecular concentration of the narcotics in the fatty lipoids of the brain which is established when the narcotic limit concentrations are reached and which prevails at the moment of narcosis. If C is the volume percentage of narcotic in air at 760 mm pressure, L is the solubility coefficient, R = 24.1 at 20° is the gas constant, C_{lip} is the concentration of the narcotics in mols, in a litre of fatty lipoid, then we obtain:

$$C_{lip} = \frac{1}{R} \cdot \frac{C}{100} \cdot L .$$

The values are summarised in the last column: C_{lip} is constant within the limits of error.

Our results lead to the following conclusion: chemically inert inhalation anaesthetics have a narcotic effect on mice if they are inhaled in such concentrations as to produce a content of 0.06 mols per litre in the fatty brain lipoids.

This law, which has been worked out purely experimentally, for lipoids with a dissolving capacity similar to liquid fat can be extended most probably to the brain lipoids as a whole. The total amount of the brain lipoids in the living brain has, in fact, the same dissolving capacity for narcotics as has liquid fat: at the moment of narcosis the same chloroform content has been obtained analytically as has been calculated on the basis of the coefficient of solubility in oil.

Frâulein Frison and M. Nicloux [5] have discovered that the chloroform contained in the brain of narcotised dogs varies in amount quite definitely as between the grey and white matter, but that there is a constant ratio between the chloroform taken in and the quantity of lipoid in these matters. Their explanation of this is that the chloroform is absorbed almost exclusively by the lipoids, a hypothesis which is very likely since the distribution coefficient of chloroform oil/water is equal to 70 and the distribution coefficient lipoid/water would probably be similar in magnitude, so that when equilibrium prevails, almost all the chloroform must be in the lipoids. In the following survey, compiled by Frison and Nicloux, we have added in the last column the molar concentrations in the lipoids.

	Matter	$CHCl_3$ in g to 100 g fresh tissue.	Amount of lipoid ($CHCl_3$ extract) to 100 g fresh tissue	$CHCl_3$ in g to 100 g lipoid	$CHCl_3$ in mols to 1 l lipoid.
Dog 10 kg.	grey	0.039	8.6	0.45	0.04
	white	0.0656	15.2	0.43	0.04
" 7 "	grey	0.0385	8.2	0.47	0.04
	white	0.071	16.9	0.42	0.04
" 17 "	grey	0.0375	8.7	0.43	0.04
	white	0.060	14.8	0.40	0.03
" 11 "	grey	0.038	8.4	0.45	0.04
	white	0.060	14.6	0.41	0.03

The value of 0.04 mols per litre lipoid found by analysis agrees satisfactorily with the value of 0.05 ± 0.01 which we found with chloroform.

BEHAVIOUR OF COMPOUNDS VERY DIFFICULT TO DISSOLVE IN WATER

Since transport to the brain lipoids is effected by way of the blood path, equilibrium between the lipoid-gas phase will be established very slowly in the case of compounds which dissolve with difficulty in water. If, now, compounds of this type are also gradually burnt up by the organism, the true statistical equilibrium can never be achieved and a static condition sets in (dynamic equilibrium) with the result that the concentration in the gas-phase is greater than should be assumed on the basis of the solubility coefficients. In such cases the concentration of narcotic in the inhaled air must be made greater in order to reach a concentration of 0.06 in the lipoids. Such a case is probably presented by amylene which has a higher solubility coefficient than ethyl ether but has a slightly weaker narcotic action.

THE INFLUENCE OF TEMPERATURE

Most inhalation anaesthetics are known to be more effective at lower temperatures than at higher ones. In particular it has been shown by Overton that tadpoles can be narcotised at 17° by air with 0.07 g of ether to a litre, while at 30° narcosis is not effected until the content is 0.15 g per litre. It has also been shown by Frey [6] that mice need twice the concentration by volume of ethyl chloride for narcosis than is required for tadpoles at 17°. In our opinion this phenomenon can be explained by the rise in the solubility coefficient with falling temperature. We determined the solubility coefficients for a number of narcotics in oil at 17° and give below a summary of the values for L 17° and L 37° together with the quotient $\frac{L\ 17^\circ}{L\ 37^\circ}$:

	L 17°	L 37°	$\frac{L\ 17^\circ}{L\ 37^\circ}$
Nitrous oxide	1.5	1.4	1.1
Dimethyl ether	18	11.6	1.6
Methyl chloride	23	14.0	1.6
Ethyl chloride	72	40.5	1.8
Diethyl ether	110	50.2	2.2
Chloroform	470	267	1.7

According to this it can be expected, on the basis of the lipoid theory, that at 17° the nitrous oxide is only a little more effective as a narcotic than at 37° while the others have a narcotic action 1½ to 2 times as strong.

THE SIGNIFICANCE OF ADSORPTION

While high-molecular narcotics may possibly become concentrated, "adsorbed" at the boundary surfaces within the cells, this is not probable in the case of the easily volatile inhalation anaesthetics. In the case of nitrous oxide [7] for example, we know that it is not adsorbed by the strongly adsorbent colloid suspensions and solutions of iron hydroxide,

starch, dextrin, gelatine, glycogen and egg or serum albumin; we also found from a provisional experiment that gaseous ethyl chloride is absorbed by an emulsion of oil-albumin solution in accordance with its coefficients of solubility in oil and albumin solution, that is to say it is not appreciably adsorbed. It also appears, from all the works dealing with the absorption of low-molecular narcotics by animal cells or tissues with the concentrations or partial pressures involved in narcosis, that Henry's law holds good, that is to say no appreciable adsorption takes place [8]. Finally, we see from the above-mentioned comparison between the chloroform content of the brain, determined analytically by Frison and Nicloux, and the content calculated on the basis of the solubility coefficients, that the experimentally found content is equal to, or somewhat less (0.04 mol/litre lipoid) than the value (0.05 ± 0.01) calculated from the solubility coefficients, but it is not greater, as ought to be the case if the chloroform had been taken in, not only through solution but also, to a considerable extent by adsorption.

Thus adsorption has no appreciable influence on the amount of inhalation anaesthetic taken up by the tissues.

THE CONCENTRATION OF NARCOTICS IN THE LIPOIDS OF NARCOTISED TADPOLES

The striking constancy which we discovered in the narcotic concentration in the brain lipoids of mice led us to make the corresponding calculations for the previously existing values of H. Meyer, Baum and Overton for narcotic limit concentrations and distribution coefficients. The narcotics, which cover almost all the available experimental material, are set out in Table 3 in order of effective strengths; C_{lip} is shown in Column 3. The limits of error have to be drawn much wider here than in our experiments; the distribution coefficients calculated according to Overton from solubility in oil and water agree poorly in most cases with those obtained directly by Baum and there is also a marked difference in the values for the narcotically effective concentrations. In the case of trional, for example, calculations based on Baum's values give C_{lip} = 0.006 mols per litre, while with Overton's we get C_{lip} = 0.11. Hence the values for C_{lip} simply permit some assessment of order of magnitude and errors of 300% must be allowed for. There is therefore an obvious need for verification and extension of the existing factual material.

As can be seen, nearly all the values of C_{lip} fluctuate between 0.01 and 0.13 mols per litre, although the final member in the series is a hundred thousand times as effective as the first member and the series embraces substances from the most widely varying classes. There are striking exceptions in chloral hydrate, bromal hydrate and butyl chloral hydrate; It is probable that an adequate explanation is offered by the possibility of slight splitting up into the very effective chloroform or a dissociation into lipoid-soluble chloral and water. Some acid amides also stand out from the series, their narcotic power having, perhaps, some other special cause.

On the whole the values of C_{lip} fluctuate about the value 0.05, which approximates very closely to that of 0.06 found for mice.

CONCLUSIONS

We think that our experiments and the present discussion have established the probability that narcosis always sets in when any chemically inert substance penetrates into the cell-lipoids in a definite molar concentration.

	Narcotic conc. for tadpoles in mol/litre water acc. to		Distr. coeff. oil/water acc. to		Conc. of narcotic in mol/litre lipoid.
	Overton	Meyer & Baum	Overton	Meyer & Baum	
Alcohol	0.3	0.5	0.03	0.03	0.01 —0.02
Methylurethane		0.04		0.04	0.02
Acetone at 3°		0.03		0.14	0.04
tert. butyl alcohol	0.13			0.18	0.02
Propyl alcohol	0.11			0.13	0.01 —0.02
Amylene hydrate	0.057			1.0	0.06
Valeramide	0.05		0.07		0.004
Ethylurethane	0.04	0.03	0.05	0.14	0.002—0.006
Ethyl ether	0.024			2.4	0.05
Paraldehyde	0.023		3		0.07
Diacetic acid ester	0.019		4		0.08
Acetal	0.012		8		0.09
Acetanilide	0.0094		2		0.02
Methacetin	0.009		2		0.02
Sulphonal	0.009	0.006	4.5	1.1	0.007—0.04
Tetronal		0.0018		4	0.007
Trional	0.007	0.0013	16	4.5	0.006—0.11
Chloral hydrate	0.006	0.025		0.22	0.001—0.005
Bromal hydrate		0.002		0.7	0.001
Butyl chloral hydrate		0.002		1.6	0.003
Phenol	0.0053		4		0.02
Benzamide	0.003	0.007		0.44	0.003
Phthalide	0.0043		3.3		0.01
Ethyl chloride	0.004			24	0.10
Vanillin	0.0033		3		0.01
Phenacetin	0.003		4		0.01
Guiaiacol	0.003		30		0.09
Ethyl bromide	0.0023	0.0031		37	0.08— 0.11
Salycyclamide at 30°		0.002		14	0.03
Piperonal	0.002		100		0.2
Chloroform	0.0012			70	0.08
Hydroquinone dimethyl ether	0.0009		300	160	0.27— 0.14
Chloretone		0.0008		22.8	0.02
Phenylurethane	0.0006		150		0.09
Cumarin	0.0006		10?		0.006
Carbon disulphide	0.0005			50	0.03
Menthol	0.0001		250		0.03
Thymol	0.000055		600		0.03
Phenanthrene	0.0000037		40000		0.15
				Average	0.05

This "critical concentration" depends on the kind of animal, the type cell, etc., but on the whole it is independent of the properties of the narcotic.

This leads us on to the conclusion that narcosis is a - presumably indirect - consequence of this dissolution in the lipoids. It is not possible, however, to decide the nature of the immediate, direct effect of solution which, in turn, has a direct influence on the narcosis. In view of the distinct differences in reactivity and constitution of the narcotics which then have similar effects, it cannot possibly be a chemical reaction. We must rather assume that it is a physical change of state in the cell-lipoids and hence in the cell, which is brought about uniformly by homomolecular dissolving, in a similar manner to that in which the point of solidification of liquids is depressed by homomolecular additives, by the same amount. Whether this involves a uniform lowering of solubility for oxygen, or a kind of lowering of the melting point, or a uniform change in the degree of imbibition, ion permeability, etc. is beyond the scope of this treatise to decide.

SPECIFIC SECTION

DETERMINATION OF THE EFFECTIVE CONCENTRATIONS OF INHALATION ANAESTHESIA

Two white mice are placed under a bell jar of 22 l capacity (Figure 1) which is slid on to a glass plate and is fitted with a smoothly working agitator. A small measuring cylinder with a known quantity of liquid anaesthetic - possibly pre-cooled by a freezing mixture - is then placed under the bell jar in such a way that it can be sent round by the blades of the agitator. Through the starting up and rotatory motions the liquid is quickly vaporized and a corresponding quantity of air escapes at a. In some cases the liquid is also dropped on to the floor of the bell jar through a long pipette. When working with gases the mice are first placed under the small bell jar c, the gas introduced cautiously from a calibrated gas reservoir through b, so that only air escapes through a, after which the bell jar c is lifted quite high, by means of a thread, and then the agitator is started up. At first the agitation is carried out for 3 — 5 minutes and subsequently every 5 — 10 minutes for a short time. In the summary which follows the undermentioned abbreviations are used:

t - temperature
Z - duration of experiment
N - narcotic content of the air in vol.%, referred to 760 mm.
lgl - light disturbance of balance (staggering)
sgl - severe disturbance of balance (falling and rising again)
lN - light narcosis (remains lying on the side or back, does not move when prodded with the rotatable tube b).

DIMETHYL ETHER. t - 21°

N - 10% Z - 30' After 15' lgl, after 30' lgl, otherwise quite lively.

N - 12% Z - 30' After 5' lgl, after 20' one, after 25' the other mouse in lN. On removal, immediate recovery.

N - 13% Z - 20' After violent state of excitement lasting 3 — 4' at 5' lgl; after 10' one, after 15' the other in lN.

Effective limit concentration: 12.0% ± 2%.

DIETHYL ETHER. t - 20°

N - 1.0% Z - 60' No effect

N - 2.3% Z - 60' After 30' lgl, nothing else

N - 3.2% Z - 40' After 35' one in lN, the other sgl

N - 3.4% Z - 60' After 8' lgl, one after 20' in lN, the other only sgl, even after 60'.

N - 4% Z - 60' In the first 8' violent state of excitement, after 8' lgl, after 20' one, after 28' the other mouse in lN.

Limit concentration: 3.4% ± 0.3%.

Beat (9) gives 3.9%.

ETHYLENE OXIDE. t - 21°

N - 4.0% Z - 30' For 30' no signs apart from drowsiness. Both mice died in the night after the experiment.

N - 5.8% Z - 60' After 35' lN. On removal both mice revived but remained listless and apparently partially paralysed and died in the night.

Limit concentration: 5.8% ± 1.8%.

METHYL CHLORIDE. t - 21°

N - 5.0% Z - 30' Only lgl after 30'. Drowsiness. The mice remained drowsy and died after a day.

N - 6.5% Z - 35' Soon lgl; after 30' one mouse in lN, the other sgl. Both dead after a day.

Limit concentration: 6.5% ± 1.5%.

ETHYL CHLORIDE. t - 25°

N - 3.0% Z - 30' After 30' only drowsiness.

N - 4.2% Z - 150' For 10' excited, after 20' lgl, after 150' only staggering and drowsiness.

N - 5.0% Z - 30' Excitement for 10', after 30' one mouse in lN, the other in convulsions.

Limit concentration: 5.0% ± 0.8%.

Frey (10) working at 20° gives 3.6% as the critical concentration - referred to 760 mm.

/Methyl bromide ....

METHYL BROMIDE. t - 19°

N - 20% Z - 30' After 30' lying on the floor, breathing heavily, dead one hour afterwards.

N - 2.3% Z - 30' First excitement, after 8' lgl, then heavy breathing, very drowsy. Dead soon afterwards.
The high toxicity thus prevents determination of exact limit concentration, but the lgl shows that the limit concentration must lie round about 3-4%.

ETHYL BROMIDE. t - 19°

N - 0.8% Z - 120' No effect

N - 1.2% Z - 120' After 15' lgl, after 120' only sgl and heavy breathing.

N - 1.6% Z - 120' Violent excitement at first, after 15' lgl, after 120' only sgl.

N - 1.9% Z - 40' After 35' one mouse in LN, the other breathing slowly, very drowsy. Soon afterwards both dead.

Limit concentration: 1.9% ± 0.3%.

Bert gives 1.65%.

CHLOROFORM. t - 20°

N - 0.44% Z - 30' After 12' sgl, after 30' LN.

N - 0.6% Z - 30' After 8' lgl, after 15' sgl, after 23' one, after 26' the other mouse in LN.

Limit concentration 0.44% ± 0.04%.

Bert gives 1.2% Wittgenstein (11) 0.44% at 20°.

METHYLAL. t - 22°

N - 2.4% Z - 30' Only slight staggering, after the experiment violent excitement, wild running around.

N - 2.8% Z - 30' After 30' LN. After the experiment state of violent excitement.

N - 3.1% Z - 30' After 10' sgl, after 30' LN. On removal very rapid revival and wild running round.

Limit concentration: 2.8% ± 0.4%.

DIMETHYLACETAL. t - 22°

N - 1.5% Z - 45' Only after 40' lgl.

N - 1.9% Z - 30' After 10' lgl, after 27' LN. Rapid revival, violent excitement.

Limit concentration: 1.9% ± 0.3%.

DIETHYL FORMAL. t - 22°

N - 0.47% Z - 60' No effect

N - 1.0% Z - 60' After 35' one, after 45' the other in 1N. Quick revival.

Limit concentration: 1.0% ± 0.2%.

AMYLENE. t - 21°.
(Industrial, freshly distilled)

N - 3.0% Z - 120' No effect

N - 4.0% Z - 30' No effect

N - 4.0% Z - 120' After 55' both mice in 1N.

N - 4.5% Z - 120' After 45' both mice in 1N. Revival rapid, recovery speedy. Narcosis equilibrium seems to set in more slowly here than with the other compounds, which is probably attributable to the low solubility of amylene in water and the resulting slowness in its passage.

Limit concentration: 4.0% ± 1.

Bert gives 4.7%.

n. PENTANE. t - 21°

N - 3.3% Z - 60' No effect.

N - 4.5% Z - 60' No effect.

N - 10% Z - 60' After 60' very drowsy, lgl, heavy breathing.

N - 15% Z - 25' Heavy breathing, after 20' one, after 25' the other mouse dead. Here, too, clearly because of the low solubility of pentane in water, equilibrium is established very slowly. Exact determination was prevented by the toxic action. It appears to lie between 10 and 15%.

1.2 ETHYLENE BICHLORIDE. t - 21°

N - 0.74% Z - 30' After 30' only lgl.

N - 0.88% Z - 30' After 20' lgl, after 25' sgl.

N - 0.95% Z - 30' After 15' lgl. After 20' one mouse in 1N, the other sgl, heavy breathing, drowsy. Speedy revival with no harmful effects.

Limit concentration: 0.95% ± 0.1.

Wittgenstein (12), gives 0.97% at 20°.

Of the newly investigated compounds only the three acetals, apart from dimethyl ether, are tolerated without harm. The toxicity of the halogen alkyls increases in the same sequence as their capacity for saponification in alcohol and hydrogen halide: ethylene bichloride

very difficult to saponify), chloroform, ethyl chloride, methyl chloride, ethyl bromide, methyl bromide. We therefore attribute the toxic action to the splitting off of acid in the cell.

Perhaps the high toxicity of ethylene oxide is due to the intracellular formation of glycol by the addition of water and subsequent oxidation to oxalic acid. We are unable to learn whether glycol is toxic within the cells because, owing to its insolubility in lipoids, we were totally unable to introduce it into the cell.

DETERMINATION OF THE COEFFICIENT OF SOLUBILITY OF GASEOUS NARCOTICS IN OIL.

1. GASES AND VERY EASILY VAPORIZABLE SUBSTANCES.

As we had to work with reduced pressure, we were unable to determine the absorption in oil gas-volumetrically, in the usual way, but measured the reduction in pressure in a constant volume of gas which resulted from shaking up with oil.

The absorption vessel (Figure 2) has a capacity of about 300-400 cc. and is closed by the three-way cock I and the single cock II, which has a pipette P ground on to its connection piece s. The ground-in joints of the taps must be very long and perfect. They are lubricated with the smallest possible quantity of "Ramsay grease". The vessel can be clamped into a weighing device, in the thermostat which is electrically heated and controlled, and well shaken.

To fill the vessel with gas, s is closed with a rubber stopper, II is opened, the vessel evacuated through k', II - of which the bore is now free from air - is closed and then the whole vessel is evacuated at 40° for a further 20 minutes to about $\frac{1}{2}$ — 1 mm, in order to remove completely the adhering film of water. The tap I is turned through 180° so that k' and k'' are connected. 5 cc. of the liquid narcotic are made to boil vigorously for 2 minutes in a $\frac{1}{2}$ — 1 glass bulb, fitted with a 5 mm. wide connecting tube through which the vapour flows out of the bulb. The connecting tube is then attached to k', so that the vapour blows through k' and K", whereupon, by the rapid turning of I, the required quantity of vapour is admitted to the vessel. I is then closed, the vessel placed in the thermostat and the pressure read off after $\frac{1}{2}$-hour. For this purpose k' is connected with the manometer (Figure 3), k' is filled with mercury by lifting the levelling vessel, tap I is closed completely by being rotated through 90°, the mercury is lowered and then tap I is opened from the vessel to the manometer. The mercury is adjusted on to the 0-mark and the difference in pressure in the two limbs p_1 and p_2 is read off from the mirror scale sp: this - taken away from the barometric reading - gives the pressure of the gas. The gas is then driven back from the 0-mark to tap I, tap I is closed, the absorption vessel taken off and the oil is then introduced.

Gases such as dimethyl ether, etc., were introduced in a similar way, from a glass gas reservoir in which calcium chloride solution was used as the sealing-off fluid.

The oil was olive oil of a specific gravity 0.91; on many occasions sesame oil was used, specific gravity 0.91 which possessed the same absorption capacity, as was proved by special experiments. The oil was freed from air by evacuation for several hours by means of the mercury-vapour pump at 100°. A small beaker with oil, the pipette P and a piece of filter paper were then weighed together accurately to 0.01 g.

P is inserted in s, and filled with oil, the oil being then introduced into the absorption vessel by cautious turning of the tap. The pipette is placed in the beaker, the oil remaining in s is carefully absorbed with the weighed filter paper and everything is weighed back together. When account has been taken of the oil remaining in the bore of the tap and the specific gravity of the oil, the volume of oil introduced into the vessel is exactly known. The apparatus is now shaken up in the thermostat for 2 — 3 hours, the pressure then read off as above, and as a further check the shaking is continued for another 2 hours, after which the reading is taken again. In order to achieve equilibrium from the other side also, the shaking procedure was repeated at a lower temperature, so that more was absorbed, the shaking was again performed at the experimental temperature and the reading taken.

Corrections. If the vessel is not absolutely evacuated before the gas is introduced, but there is still about $\frac{1}{2}$ — $1\frac{1}{2}$ mm pressure in it, this pressure must be subtracted from all the measured pressures. Further, since it is not the pressure for volume g of the vessel, which is measured, but for volume g plus the volume k of the capillary ka up to the O-mark in the manometer, the pressure was reduced to the volume g by multiplication by $g+k/g$ (in one case, e.g.,

$$\frac{308.4 + 1.3}{308.4} = 1.004.$$

Where the volume of oil, n, was considerable, the multiplication factor was taken as

$$\frac{g - n + k}{g - n}.$$

The table contains the values which have been corrected in this way.

Calculation. If p is the read and corrected initial pressure in mm Hg, for a volume v of the vessel, p_1 is the final pressure after absorption, n the volume of oil, then the total amount of gas $= \frac{1}{R \cdot T} p.v.$, the amount of gas remaining after absorption in a volume of gas $v - n = \frac{1}{R \cdot T} \cdot p_1(v-n)$, the amount remaining in the oil is equal to the difference between the two

$$= \frac{1}{R \cdot T} (p \cdot v - p_1[v - n]).$$

The solubility coefficient is equal to the product

$$\frac{\text{amount dissolved}}{\text{amount of gas}} \cdot \frac{\text{volume of gas}}{\text{volume of oil}},$$

thus:

$$L = \frac{p \cdot v - p_1(v - n)}{p_1(v - n)} \cdot \frac{v - n}{n} = \frac{p \cdot v - p_1(v - n)}{n \cdot p_1}.$$

Substance	No.	Temperature in °C	Total volume in cc.	Initial pressure (corrected) in mm Hg	Volume of oil in cc.	Final pressure (corrected) in mm Hg	Solubility coefficient	Mean
		t	v	p	n	p_1		
Nitrous oxide (Olive oil)	1	37	261.4	603.5	28.34	576.7	1.44	
	2	37	261.4	607.5	29.10	577.7	1.47	
	3	37	261.4	621.6	19.37	606.7	1.34	
	4	37	261.4	632.2	31.32	608.4	1.34	1.40 ± 0.06
Dimethyl ether (Olive oil)	1	37	308.4	562.5	11.71	401.8	11.5	
	2	37	308.4	559.5	9.39	423.8	11.5	
	3	37	308.4	667.0	10.39	484.6	11.6	11.5 ± 0.1
	1	17	308.4	661.0	17.39	340.0	17.7	
	2	17	308.4	686.0	17.17	349.0	18.7	17.9 ± 0.2
Diethyl ether (Olive oil)	1	37	260.5	273.5	5.85	133.2	48.0	
	2	37	260.5	244.0	4.10	137.3	50.2	
	3	37	308.4	262.5	4.89	148.6	49.2	
	4	37	260.5	316.0	4.79	159.8	54.3	
	5	37	260.5	308.5	4.15	176.4	48.1	
	6	37	260.5	443.5	6.99	191.9	49.6	
	7	37	308.4	501.0	7.60	215.9	54.5	50.2 ± 4
n. Pentane (Sesame oil)	1	37	405.4	161.7	10.38	84.3	36.8	
	2	37	405.4	196.2	12.57	91.3	37.8	37.3 ± 0.5
Amylene (Sesame oil)	1	37	405.4	244.0	8.50	98.8	71.5	
	2	37	405.4	555.0	18.16	140.4	67.0	69.0 ± 2.0
Methyl chloride (Olive oil)	1	37	308.4	189.0	14.5	122.0	13.0	
	2	37	308.4	212.0	8.89	153.1	14.3	
	3	37	308.4	328.0	10.44	229.5	13.6	
	4	37	308.4	610.5	6.28	480.5	14.3	
	5	37	308.4	750.5	6.22	589.5	14.5	14.0 ± 1.0
	1	17	308.4	215.5	11.88	119.0	22.0	
	2	17	308.4	270.5	8.27	171.2	22.3	
	3	17	308.4	356.0	12.50	190.8	22.3	
	4	17	308.4	305.5	6.41	207.9	23.6	22.6 ± 1.0
Ethyl chloride (Olive oil)	1	37	308.4	423.5	14.53	149.6	39.7	
	2	37	308.4	601.5	17.69	187.3	39.9	
	3	37	308.4	594.5	15.77	195.3	41.0	
	4	37	308.4	593.5	13.21	218.9	41.0	
(Sesame oil)	1	37	405.4	181.0	9.35	92.8	42.3	40.5 ± 1
(Olive oil)	1	17	308.4	528.5	17.14	104.9	73.7	
	2	17	308.4	578.0	16.62	125.6	71.4	
	3	17	308.4	527.0	11.22	134.6	78.0	
	4	17	308.4	692.5	12.01	173.7	77.3	75 ± 3
Methyl bromide (Sesame oil)	1	37	405.4	438.5	11.72	226.2	33.5	
	2	37	405.4	480.0	10.79	267.2	31.2	
	3	37	405.4	486.0	9.76	283.9	30.8	32 ± 1.5
Ethyl bromide (Olive oil)	1	37	317.8	176.0	4.34	78.3	92.1	
	2	37	317.8	202.0	4.51	86.4	95.2	
	3	37	317.8	212.0	3.72	99.4	97.7	
	4	37	317.8	217.0	3.75	101.4	97.5	95 ±,3

2. LIQUIDS.

L can be determined much more conveniently, although a little less exactly, by measuring the vapour pressure exhibited by the narcotics when they are dissolved in oil in a known ratio.

About 2 cc of air-free oil are put in the funnel c of the manometer Figure 4, which is filled with mercury under the usual precautionary measures and closed at H, H is then opened and a little oil drawn in by lowering the levelling bottle, H is closed again, the levelling bottle dropped right down and the tension of any impurities remaining in the oil (traces of water or air) is measured. This should not be more than 1 mm.

Substance	Boiling point in °	No.	Temperature in °	g substance in 100 cc oil	Mol per 1 oil	Vapour pressure in mm Hg	L	Value of L on which calculations are based
Chloroform	61	1	37	5.37	0.449	32.5	268	
		2	37	7.27	0.608	44.0	266	
		3	37	9.25	0.777	56.5	262	265 ± 3
		1	17	5.44	0.445	17.0	513	
		2	17	7.36	0.615	27.0	437	
		3	17	9.58	0.801	33.0	465	470 ± 40
Ethylene bichloride	55	1	37	2.45	0.253	38.0	129	130 ± 10
		2	37	3.47	0.358	50.0	139	
Ethyl ether	35	1	17	1.07	0.144	28.0	99	
		2	17	1.95	0.263	42.0	120	
		3	17	2.68	0.362	62.0	112	
		4	17	7.21	0.974	117.0	160	110 ± 10
Ethylene oxide	13.5	1	37	0.54	0.123	8.7	23	
		2	37	0.95	0.216	11.6	36	30 ± 5
		3	37	1.73	0.393	21.0	36	
Methylal	41 to 44	1	37	2.15	0.283	74.0	74	
		2	37	3.47	0.457	101.0	87	75 ± 5
Dimethyl acetal	64	1	37	1.97	0.219	48	88	
		2	37	3.58	0.375	60	121	
		3	37	4.20	0.466	65	138	100 ± 10
Diethyl formal	85 to 87	1	37	1.27	0.122	20	118	
		2	37	1.44	0.138	21	127	
		3	37	3.13	0.300	37	157	120 ± 10
Amylene	37	1	37	1.82	0.260	73	63	63 ± 6

The oil is then expelled and replaced by a solution of narcotic in oil, freshly prepared by weighing, with which a rinsing operation is carried out by repeated raising and lowering of the levelling bottle. The tension of the solution is determined while the complete manometer is in a thermostat. Stability is reached in about ½-hour. All the narcotic can be removed again by repeated rinsing with pure oil without any need for cleaning the manometer. Sesame oil only was used.

In the case of substances with a somewhat higher boiling point it is possible to observe an increase in the solubility coefficient with the concentration, for fairly high concentrations; diethyl formal is an example. The phenomenon is connected with deviation from the gas laws.

APPROXIMATE CALCULATION OF THE DISTRIBUTION COEFFICIENT OF A FEW SUBSTANCES FOR $\frac{\text{OIL}}{\text{WATER}}$

In the saturated solution of a substance which is difficultly soluble in water, the tension of this substance is equal to the tension of the free substance itself. (More correctly, equal to the tension of the free substance saturated with water). Knowing the latter, and also the solubility, it is possible to calculate from these the equilibrium between aqueous solution and gas phase, i.e. the solubility coefficient. By dividing the coefficient of solubility in oil - determined earlier - by that in water we obtain the distribution coefficient oil/water. All values are valid for 20°.

Substance	% content of solution in water	Vapour pressure	L_{H_2O}	L_{oil}	$T\ \frac{oil}{water}$
Carbon disulphide	0.22	300	1.7	ca. 80	50
Chloroform	0.62	160	5.9	400	70
Ethyl chloride	-	-	2.1	65	30
Ethyl bromide	1	387	4	ca. 150	35
Ether	6.7	360	45	110	2.4

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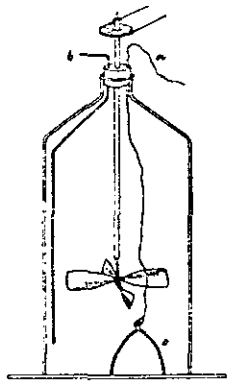


Fig. 1.

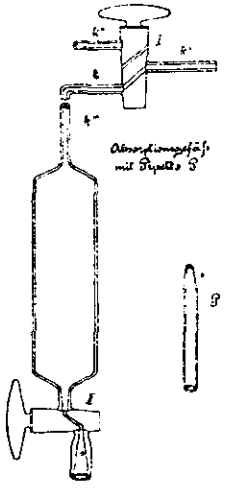
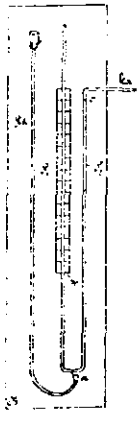


Fig. 2.



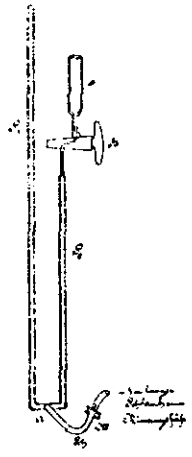


Fig. 4

ACSIL/ADM/58/122

A.C.S.I.L. Translation No. 920

THEORY OF NARCOSIS BY INHALATION ANAESTHETICS

Second Communication

Narcosis by inert gases under pressure

K. H. Meyer and H. Hopff

Zeitschrift für Physiologische Chemie, 126 (1923) 288-298

(From German)

DEPARTMENT OF RESEARCH PROGRAMMES AND PLANNING

ADMIRALTY

March 1958

Theory of Narcosis by Inhalation Anaesthetics

Second Communication

Narcosis by inert gases under pressure
Kurt H. Meyer and Heinrich Hopff
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Some time ago, one of us in collaboration with Hans Gottlieb-Billroth[1]* compared the narcotic efficiency of a series of inhalation anaesthetics with their coefficient of solubility (absorption coefficient) in lipoid substances. We found an exact proportionality between narcotic efficiency and the solubility coefficient. The purely experimental result was that "chemically inert inhalation anaesthetics have a narcotic effect on mice, when they are inhaled in such concentrations as to ensure a content of 0.06 mole per litre in the fat-like brain lipoids".

At that time we only experimented with gases and vapours, the solubility of which in oil, which was used as model of a lipoid, was greater than that of nitrous oxide, and which accordingly were narcotically effective in lower concentrations.

We then thought that it would be interesting to find out whether gases of lower solubility coefficient than nitrous oxide follow the law which we had discovered. From what we had learned, they should have a narcotic effect, provided steps were taken to ensure that the critical molar concentration of 0.06 mol per litre was present in the lipoids. This should be possible merely by raising the pressure.

Experiments with Methane

We chose methane as a typical chemically inert gas, which on the one hand has no special poisonous effect, and on the other hand has a chemical constitution, which allows one to expect a certain solubility in lipoids. Just as in our earlier work, we determined first the amount of concentration necessary to produce narcosis in the respiratory air, and secondly the solubility of the gas in olive oil, and calculated from both results the molar concentration of methane, which, at the moment of narcosis, was present in the fat-like lipoids.

We first experimented with a mixture of 80% methane and 20% oxygen at atmospheric pressure, but were unable to confirm the "intoxicating" effect of the methane; on the contrary, the mice remained completely unaffected by it for hours.

For these, as in subsequent experiments, we used methane, which we produced from aluminium carbide with water and which we washed with caustic soda. The compressed methane, to be bought commercially, contains poisonous impurities, and possibly also small quantities of carbon monoxide, and consequently should not be used for biological experiments.

We now passed to experiments under pressure, carried out with apparatus most kindly supplied by Herr H. Bart of Heidelberg; for which we desire to express our grateful thanks. The animals for our experiments were kept in a thick-walled, cylindrical glass vessel, of about 300 cubic centimetres capacity, tested under pressure, the top and bottom of which could be sealed pressure-tight by metal covers, to which were fixed tubes leading to the pressure gauge and the

/compression ...

* For references, see end.

compression pump - the animals were placed in the container, which had previously been filled with air, and which was then closed. Methane was then pumped in from a gas-holder by means of a small hand compressor. The absolute pressure, as read off, is then equal to the partial pressure of the methane.

Time Mins.	Pressure read in atm. = partial pressure of methane	
I	Mouse: small specimen	
2	1.5	No symptoms.
3	2.5	Staggering.
5	3	Lies on its back and struggles on shaking the container.
7	3.5	Narcosis: hardly any reflexes perceptible.
9	4	Deep narcosis: no reflexes at all.
10	2.5	Narcosis: respiration very much slowed down.
14	0	Taken from the container: recovers in a few minutes.
II	Mouse: strong specimen	
4	2.5	Staggering.
6	3	"
8	3.15	Violent staggering.
9	4	Lying on its back: reflexes weak.
10	4.5	Narcosis: no reflexes.
11	2.5	Conscious again.
14	0	Taken from the container: creeps rapidly away.
III	Frog (esculenta)	
6	5	No effect.
7	6	Sluggish movement: allows itself to be placed on its back.
8	7.6	Narcosis: struggles to move.
12	7.6	Deep narcosis: no reflexes.
15	-	For three minutes the pressure was allowed to drop and the insensible creature removed from the container. Skin reflexes disappear: in two minutes the creature is awake and lively.

Thus, methane is narcotic for mice in a concentration of 3.5 to 4 atmospheres. For frogs, in our case, it is 7 to 8 atmospheres: thus, in the latter case, a concentration of narcotic, double that used for mice, is necessary.

The solubility of methane in oil, according to the system outlined above, should be reckoned at 0.54 at 37°C, according to the formula previously given:-

$$C_{lip} = \frac{1}{R} \cdot \frac{C}{100} \cdot L$$

C_{lip} = concentration in fat-like lipoids.

R = 24 the gas constant at 20°C.

C = Narcotic content in the air at 760 mm. per cent. by volume.

L = Solubility coefficient.

Which works out as: (C here = 3,700, corresponding to 3.7 atmospheres).

$$C_{lip} = \frac{1}{24} \cdot \frac{370}{100} \cdot 0.54 = 0.08 \text{ (mouse)}$$

and

$$C_{lip} = \frac{1}{24} \cdot \frac{760}{100} \cdot 0.54 = 0.17 \text{ (frog)}$$

In the fat-like lipoids of the mouse, 0.08 mole of methane was thus dissolved at the moment of narcosis.

That frogs are rather less affected by the narcotic than mice seems to contradict the fact that, after being subjected to a number of narcotics such as ether, they are more easily anaesthetised than mice. We traced this back to the solubility of the narcotics employed.

In the case of ether, for instance, the solubility coefficients, in oil at 17°C, amounted to L = 110; at 37°C to L = 50[2]. Ether therefore penetrates the lipoids at 17°C in a concentration 2.2 times as high as at 37°C, and consequently in the case of a cold-blooded creature, appears to be more active than in the case of a warm-blooded one. This will even be the case when a cold-blooded creature needs to have in its lipoids a considerably higher concentration (e.g. 1½ to 2 times as high) for narcosis than does a warm-blooded one, provided that in actual fact the former is less sensitive than the latter. On the other hand, in the case of methane, the difference in solubilities at 17°C and 37°C is negligible[3]; so that, at both temperatures where the same concentration is present in the respiratory air, rather similar quantities are dissolved in the lipoids, and thus the less sensitive creature, the cold-blooded one, is less easily narcotised.

Experiments with Nitrogen

We now turned to experiments with nitrogen, which, as is well known, has quite a small but nevertheless perceptible solubility in oil. Here, in our opinion, narcotic effects were to be expected at a corresponding pressure. The solubility of nitrogen in oil has been measured by Vernon[4] and later by Quincke[5]. Vernon found the solubility coefficient to be 0.05; Quincke, using a method which was not very accurate, gave a slightly lower figure. Consequently, the solubility is about thirty to fifty times less than it is in the case of nitrous oxide, which at 37°C amounts to 1.4 and at 18°C to 1.63[6]. We now tried to prove that by a corresponding increase in pressure narcosis could be induced by the use of nitrogen. We made a large number of experiments on the influence of compressed

air on animals and human-beings. The phenomenon, which is most striking when observations of this kind are made, is the damage which occurs when pressure is lowered, and is obviously connected with bubble formation produced by the gas which is dissolved under pressure and is suddenly expanded. On the other hand, a gradual raising of pressure does not appear to involve damage or any other phenomena.

Naturally, in our experiments, we had to eliminate as far as possible the phenomenon mentioned above, known as Caisson disease. Consequently, we dealt with small animals, in the case of which an exchange of gases can quickly be effected. Moreover, we had to select animals with a comparatively low oxygen requirement, since it is clear that the oxygen content of the air is reduced in a high degree. Nitrogen is first forced into the air, and then the mixture of one atmosphere of air and many atmospheres of nitrogen is slowly expanded. For the most part, therefore, we used small amphibious creatures for this purpose.

Apparatus

For our container we used an iron tube of 25 mm. internal diameter and 40 cm. long which was closed at one end by a conical stopper, from which a pipe ran to a pressure gauge and to an escape valve and also through a second valve to a nitrogen cylinder, in which the nitrogen was at a pressure of less than 150 atmospheres. The other end of the tube was closed by a polished glass disc 15 mm. thick, which could be sealed by means of a rubber washer and a corresponding screw joint. Before the experiment, the tube was tested under a pressure of 250 atmospheres. The creatures which were in the tube could be observed through an opthalmoscope. To improve visibility, the tube was lined inside with white smooth paper. Pressure was applied by opening the gas inlet valve, which was connected to the nitrogen cylinder, and was drawn off through the escape valve.

Experimental results

In our first experiments we were always able to produce narcosis by slowly raising the pressure, but, when it was lowered, the creatures were completely narcotised, and only revived when they had been removed from the apparatus for a considerable time. In some cases, recovery even took place when the pressure dropped to 20 atmospheres, and when it dropped still further, narcotisation again took place. This phenomenon, which we attributed to excessively rapid lowering of pressure, thereby leading to Caisson disease, was avoided when we allowed the pressure to drop very slowly, especially towards the end of the experiment. It is preferable to lower the pressure gradually to half, then to wait about 20 minutes, to lower it again for a further half for five minutes, to wait again and so forth.

The following are some of our test records.

Fire Salamander - Salamanda
Maculata - 8 cm. long

February 1921

Time in hours	Pressure in Atmospheres	
0^{00}	1	Movement.
0^{20}	8	Lively movement.

- 4 -

(Contd.)

Time in hours	Pressure in Atmospheres	
1^{00}	20 -	Movement.
1^{30}	60	"
2^{00}	90 -	Narcosis, lying on back, shaking.
2^{30}	50	" " " "
2^{50}	30	" " " "
3^{20}	25	Slowly becomes conscious.
3^{40}	20	Slow movement and crawling.
4^{20}	15	Slight movement.
4^{30}	5	No movement.
5^{30}	1	No movement: recovers after several hours.
	Two Young Salamanders (Triton Vulgaris) 4-5 cm. long May 1922	
0^{00}	1	Strong reaction to light.
0^{20}	4	Moving the head.
0^{40}	8	" " "
1^{00}	16	Crawling on the glass.
1^{20}	32	Agitation.
1^{40}	64	Weak movement.
2^{00}	90	Narcosis, lying flat on the back.
2^{20}	50	No movement.
2^{50}	25	" "
3^{20}	15	" "
3^{50}	12	Slight movement of legs.
4^{20}	10	No motion.
4^{50}	8	" "
5^{20}	6	" "
5^{50}	4	Movement of head.
6^{20}	2	Crawling in the tube.
6^{50}	1	Fresh and lively, rather inflated.

(Contd.)

Time in hours	Pressure in Atmospheres	
		Two Small Frogs
0^{00}	1	Lively movement.
0^{15}	4	" "
0^{30}	6	" "
0^{45}	12	" "
1^{00}	24	" "
1^{15}	48	" "
1^{30}	90	Movement as if tired.
2^{00}	100	Narcosis: no reaction when shaken.
2^{30}	60	"
2^{50}	40	"
3^{20}	30	Movement.
4^{00}	25	Lively movement.
4^{20}	20	" "
4^{50}	15	" "
5^{10}	12	" "
5^{30}	10	" "
5^{50}	8	" "
6^{10}	6	" "
6^{30}	4	Slow "
6^{50}	2	Lively "
7^{10}	1	One frog hops from the tube, the other breathes, does not move, reacts when stimulated. Fully recovered after half an hour. Next day very lively.

During our experiments with insects (Blatta Orientalis and Blatta Germanica), we were unable to bring back to consciousness the creatures which had been narcotised at 90 atmospheres, whilst still in the pressure tube. Only when exposed to fresh air, did they wake up after some 10 minutes. We attributed this to the high oxygen requirements of the creatures, which could not be satisfied when pressure was reduced. The experiments prove that in actual fact, as we had expected, nitrogen under high pressure induces narcosis, a fact which is not yet generally known. There is no physical or biological reason why pressure alone should be responsible for narcosis. Consequently, we believe that, in the case of the phenomenon thus observed, we must more or less adopt the same explanation as in the case of narcosis by nitrous oxide: i.e., solution of nitrogen in the lipoids in the narcotically

effective molar concentration.

As regards the quantitative results of our work, it is possible to calculate on the basis of the absorption coefficient of 0.05 determined by Vernon that at a pressure of 90 atmospheres 0.18 mol must be dissolved in the fatty lipoids. Accordingly, we find that, in the case of both methane and nitrogen, at the moment of narcosis with an amphibious creature, there is the same molar concentration in the lipoids, i.e. 0.18 mole per litre of lipoid.

In our earlier work, we gave the following formulation of the "Lipoid theory":-

"Narcosis" definitely occurs when any chemically inert substance enters the cell lipoids in a given molar concentration. The "critical concentration" depends on the kind of creature or the kind of cell, etc., but on the whole does not depend on the nature of the narcotic itself.

The results of our experiments with methane and nitrogen confirm this theory and provide powerful support for the Meyer-Overton theory of narcosis.

Experiments with Ethylene

The experiments given immediately below arose from the desire to include in our tests types of all known very volatile or gaseous compounds. We next started experiments with ethylene.

As is known from earlier experiments by Lüssen[7], ethylene can induce narcosis in the same way as nitrous oxide. We can confirm the old experiments, and we find that, in the case of mice, a concentration of 80 per cent. by volume in the air does in fact suffice to induce narcosis.

Ethylene (White Mice)

Experimental arrangement as given earlier.

Content in air, % by volume	Temperature 18°C
70% Ethylene 30% Oxygen	After 5 minutes, slight displacement of equilibrium: after half an hour, the same condition.
30% Ethylene 20% Oxygen	After 3 minutes, slight displacement of equilibrium: after 6 minutes, lying on the back: after 10 minutes, no reflexes. Recovery a few seconds after being taken out.
90% Ethylene 10% Oxygen	After one minute, narcosis. Breathing greatly slowed down. Recovery very quick in two minutes after being taken out.

We found the solubility coefficient of ethylene in olive oil at 37°C to be 1.3 (i.e. 1 volume of oil absorbs 1.3 volumes of ethylene), whilst nitrous oxide at the same temperature has a solubility of 1.4.

From the formula

$$C_{lip} = \frac{1}{R} \cdot \frac{C}{100} \cdot L$$ (see page 13)

it may be calculated that, at the moment of narcosis, 0.043 mol of ethylene is dissolved in the fatty lipoids.

Propylene, which we then also tried is effective at about 50 to 60 volume per cent.

Propylene (Mouse)

Air content in volume %	Temperature 18°C
70% Propylene 30% Oxygen	After one minute, slight narcosis; deep slow breathing. Very quickly aroused.
50% Propylene 50% Oxygen	After one minute, lying on the back: after 8 minutes, slight narcosis.

Narcosis by Acetylene

The narcotic efficiency of acetylene has been briefly defined by Wieland(8). He showed that mice are narcotised in an atmosphere containing 60 to 65 per cent. by volume of acetylene. He found the solubility coefficient in oil to be about 1.8, which gives as a concentration in the lipoids at the moment of narcosis 0.045 to 0.05 mol per litre of lipoid. Accordingly, acetylene followes the rule we have found.

Narcosis with Carbon Disulphide

As an example of a compound with a chemical character quite different from the substances already investigated, we tested the narcotic effect of carbon disulphide vapour(9) and compared it with its absorption coefficient in oil.

Experiment
White Mouse

Content in air, volume %	Temperature 22°C
1.1	After 15 minutes, lying on its side: after 20 minutes narcosis: slow recovery.
6.8	After 15 minutes, lying on its side, breathing with difficulty: reflexes still functioning: after 30 minutes no change: two hours more, completely recovered.

Accordingly, it is possible to induce narcosis with carbon disulphide just as with chloroform. The solubility coefficient of carbon disulphide in oil was determined as 160, using the vapour tension method described in our first paper. From this, the concentration, in the lipoids at the moment of narcosis, may be estimated as being 0.07 mol per litre of lipoid.

Although carbon disulphide is a compound of quite different chemical properties, including quite a different aqueous solubility from the other compounds, it resembles in one point the other substances: it produces narcosis if it is present in a concentration in the respiratory air

such that by reason of its solubility in lipoids, its concentration in the lipoids must be 0.07 mol per litre.

Narcosis by Benzene

The narcotic efficiency of benzene has been recently determined by Führner[10], who found to be only slightly less than that of chloroform. We found the absorption coefficient of benzene vapour by the vapour tension method to be 240 at 37°C, whilst previously we had found the figure for chloroform to be 260. It seems that the creatures used for experiments by Führner were more resistant than ours, for whereas Führner gives the effective concentration for chloroform as 0.8 volume per cent (0.00032 mol per litre of air), we found, in agreement with Wittgenstein, rather more than half as much, i.e. 0.44 volume per cent. From the data given by Führner, one may calculate a concentration of 0.09 mol per litre of lipoid for chloroform, and 0.12 for benzene.

Effect of Oxygen Deficiency on Narcosis

It has long been known that the effect of narcotics may be strengthened by other influences, which in their turn exert a paralysing influence. This applies, for example, to the action of other poisons, which are not generally cell narcotics, e.g. morphine, scopolamine, and even magnesium sulphate, likewise mechanical influences and above all oxygen deficiency. Mansfeld[11] for instance states that the effect of paraldehyde is greatly increased by oxygen deficiency: the same applies to ether. Consequently, one cannot understand why Wieland, who has made the same observation, (strengthening of narcotic effect by oxygen deficiency), in the case of nitrous oxide and acetylene, finds here a difference in principle from all other narcotics. Indeed, on the basis of the influence exercised by oxygen deficiency on nitrous oxide narcosis and acetylene narcosis, Wieland says: "The experiments force one to draw a sharp distinction between the group of true "lipoid-soluble" narcotics and the group of "intoxicating"gases". In our view, Wieland's experiments show the opposite: namely, that the "intoxicating" gases in the connection under consideration behave exactly as do the other "lipoid-soluble" narcotics.

As proof of the special position of acetylene and nitrous oxide, Wieland quotes further experiments with anaerobic organisms (ascaridae), which are not intoxicated by nitrous oxide and acetylene, whereas other narcotics, e.g. a 20% solution of alcohol, do induce narcosis.

Wieland's experiments were carried out with both gases under atmospheric pressure, which is quite sufficient to intoxicate warm-blooded creatures. Worms were first intoxicated with higher doses of narcotic than those used in the case of warm-blooded creatures or tadpoles. Leeches for instance need for narcotisation four times as high a concentration of ether in the respiratory water as tadpoles do[12]. Consequently, in the case of ascaridae also, one must expect narcosis from acetylene or nitrous oxide, if the surrounding water has been saturated with acetylene or nitrous oxide under a pressure of many atmospheres[13].

The Importance of the Aqueous Solubility of Narcotics

H. Wieland attributes a decisive importance, for the production of narcosis, to the high absorption coefficient shown by both nitrous oxide and acetylene. The untenability of this theory, however, is proved by a comparison with ethylene, which has about the same narcotic effect as nitrous oxide, and a corresponding solubility coefficient in oil, but one-fifth the absorption coefficient in water.

In the following tables are listed the solubility coefficients of various narcotics in water at 30°C, and from them the relevant molar concentration has been calculated, which, at the moment of narcosis, occurs in the aqueous parts of the organism.

	Narcotic concentration in volume per cent in air (Mouse)	Solubility coefficient in water at 30°C[14]	Concentration in the aqueous portions in mols per litre
Nitrogen	9,000	0.02	0.075
Methane	370	0.028	0.004
Nitrous Oxide	100	0.50	0.02
Ethylene	80	0.98	0.003
Acetylene	65	0.84	0.02
Ethyl Bromide	2	2.47[15]	0.002
Carbon Disulphide	1.1	0.80	0.0004
Chloroform	0.44	4.17	0.0008

It is generally recognised that there is absolutely no connection between narcotic effect and solubility in water; or, more correctly, the concentration which is to be found in aqueous components during narcosis.

It emerges clearly from all the experiments that gases and vapours of very low solubility in water need a rather higher concentration to induce narcosis, than do other substances having a higher water solubility. Previously, we explained this as being due to the fact that by reason of the excessively low water solubility, transport to the brain lipoids is more difficult, so that one can hardly strike a real balance between gas phase and lipoid.

To this phenomenon we attributed the small discrepancies in the rule we discovered, which are shown by the hydrocarbons of the paraffin series. They have a narcotic effect, as Führer has recently shown, but if, for instance, we compare the absorption coefficient with their narcotic effect, we find that the latter is comparatively weak. Pentane, for example, has an absorption coefficient of 37, which is about as high as that of the ethyl chloride; but pentane is only half as powerful as the latter, since whilst we found that ethyl chloride is effective in a concentration of five per cent by volume, according to Führer a concentration of 10-13 per cent by volume of pentane is required in the respiratory air to induce narcosis in mice[16]. Of all the compounds with which we experimented, the hydrocarbons of the paraffin series had the lowest solubility in water, so that we attributed their low effect to the difficulty of transport to the lipoids, due to this low solubility. The fact is that the higher members in the series, e.g. petroleum, due to their almost total insolubility, show only slight narcotic qualities. Of great value for the understanding of these processes are more recent experiments of Führer and Teschendorf[17] on the resorption rate of various gases forced into the abdominal cavity of rabbits. The average resorption times are shown in the following table.

	Resorbed after:	Solubility in water 30%
Nitrogen	80 hours	0.02
Pentane	26 "	0.12
Methane	25 "	0.028
Nitrous Oxide	2 "	0.5
Ethyl Chloride	5 minutes	2
Ether	2 "	20

It will be at once seen that the rate of resorption and water solubility are closely related to each other, which is in good support of our view.

Summary of Results

In the following table we give a summary of the various results which we have achieved. We also give the data of Führer, to which we add the solubility coefficients we have ascertained.

It should be stressed at this point that the limits of error in estimating narcotic concentration must be regarded as being very high, that is about 20-30 per cent, and in extreme cases a little higher still. The age, the pre-history, the nutrition state of the animals under experiment, finally also the specific sensitivity of an individual animal as well as the outside temperature are all factors which may affect the results, so that average values of low limits of error may be obtained only by long series of experiments.

Species of animal	Substance	L=solubility-coefficient	C=narcotic concentration per cent by volume	Clip concentration of narcotic in the lipoid in mole per litre
Frog	Nitrogen	0.05	9,000	0.18
"	Methane	0.54	760	0.17
Mouse	Methane	0.54	370	0.08
"	Ethylene	1.3	80	0.04
"	Nitrous Oxide	1.4	100	0.06
"	Acetylene	1.8	65	0.05
"	Dimethyl Ether	11.6	12	0.06
"	Methyl Chloride	14	6.5	0.07

(Contd.)

Species of animal	Substance	L=solubility-coefficient	C=narcotic concentration per cent by volume	Clip concentration of narcotic in the lipoid in mole per litre
Mouse	Ethylene Oxide	31	5.8	0.07
"	Ethyl Chloride	40	5.0	0.08
"	Diethyl Ether	50	3.4	0.07
"	Amylene	65	4.0	0.10
"	Methylal	75	2.8	0.08
"	Ethyl Bromide	95	1.9	0.07
"	Dimethyl Acetal	100	1.9	0.06
"	Diethylformal	120	1.0	0.05
"	Ethylene Dichloride	130	0.95	0.05
"	Carbon Disulphide	160	1.1	0.07
"	Chloroform	265	0.5	0.05
Führer's experiments with mice	Pentane	37	13.2	0.19
	Benzene	240	1.2	0.12
	Chloroform	265	0.8	0.09

The following rule is clearly shown by this table:- all gaseous or volatile substances induce narcosis, if they penetrate the cell lipoids in a definite molar concentration which is characteristic for each type of animal (or better, type of cell) and is approximately the same for all narcotics. This rule applies to substances, such as nitrogen and chloroform, which differ from each other 10,000 times as regards their efficiency. It has no exception, since it has been confirmed in cases involving all generally known elements and compounds which are chemically inert and have no specific toxic effects. Consequently, we may say that there is hardly any other biological rule which rests on a surer and broader experimental basis of experiment than this one does.

It is a long way, however, from the recognition of this rule to the development of a "theory", which could explain the connection between solution in the lipoids and reversible paralysis of the functions, which is what narcosis is, and we are further from an understanding of narcosis than one would sometimes believe from reading the works of recent investigations, especially Warburg. This knowledge, however, should not prevent us from regarding the above rule as a basis for the "Theory of Narcosis" still to be developed.

Solubility Coefficients in Olive Oil[18]

(a) Gases

Substance	No.	Temp. °C	Total vol. cc	Initial pressure (corrected) mm Hg	Volume of oil cc	Final pressure (corrected) mm Hg	Solubility coefficient $\frac{p.v.-p_1(v-p)}{n.p_1(L)}$	Mean
Methane	1	37	260.5	544.0	19.42	562.0	0.55	
	2	37	260.5	518.5	14.58	531.0	0.53	0.54
Ethylene	1	37	260.5	576.6	28.48	576.5	1.27	
	2	37	260.5	595.0	23.69	595.5	1.28	1.28

(b) Liquids

Substance	Temp. °C	Grams substance in 100 cc oil	Mol per litre of oil	Vapour pressure mm	(L) sol coeff	Pressure used as basis for calculation
Carbon Disulphide	37	3.2	0.41	51	156	
		5.6	0.72	76	180	160
Benzene	37	2.7	0.35	28	240	240

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(1) K. H. Meyer and H. Gottlieb-Billroth. Zeits. f. physiol. Chem., 112 (1920) 55.

(2) Zeits. f. physiol. Chem., 112 (1920) 62.

(3) According to Carius, Liebigs. Ann. Chem., 94 (1855) 132, the solubility coefficient of methane in absolute alcohol at 17°C = 0.48, at 37°C = 0.44.

(4) Vernon, Proc. Roy. Soc., 79 (1907) 366.

(5) Quincke, Arch. f. exp. Pharm., 62 (1910) 464.

(6) Wieland, Arch. f. exp. Path., 92 (1922) 126.

(7) Lüssen. Thesis, Bonn, 1885. For literature, see Kunkel, Handbuch der Toxikologie.

(8) Wieland, Arch. exp. Path. u. Pharm., 92 (1922) 96.

(9) For the intoxicating effects of carbon disulphide, see Lehmann, Arch. f. Hygiene 20 (1894) 26; also Harmsen, Vierteljahrschrift für gerichtliche Medizin, 3rd Series, 30 (1905) 149.

(10) Führer, Biochem. Zs., 115 (1921) 235.

(11) Mansfeld, Pflügers Arch., 129 (1909) 69.

(12) Winterstein, Die Narkose.

(13) This actually the case, as was found by H. Bart, independently of us (reference made at the Conference of Naturalists in Leipzig, 1922).

(14) Winkler, Z. physik. Chem., 55 (1906) 353; Chem. Ber. 34 (1901) 1,417.

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(17) Führer and Teschendorf, D. med. Wochenshr. No.46 (1921) and Arch. f. exp. Path. 92 (1922) 302.

(18) For further details regarding calculation and method, see Zeits. f. phys. Chem., 112 (1920) 71.

The Opposing Physiological Effects of High Pressures and Inert Gases

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LANCASTER PRESS, INC., LANCASTER, PA.

Reprinted from FEDERATION PROCEEDINGS
Vol. 36, No. 5, April, 1977

The opposing physiological effects of high pressures and inert gases[1]

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The response of mammals to elevated ambient pressures has to be considered in the context of the physiological properties of the gases breathed. Because of the toxic properties of hyperbaric oxygen (24) an inert gas diluent is generally included in a diver's breathing mixture. The use of nitrogen in this role causes euphoria and an impairment of higher mental processes that becomes more and more serious at depths deeper[2] than 30 m (1). These symptoms of nitrogen narcosis bear some similarity to those in the early stages of anesthesia, and studies on mice show nitrogen produces complete anesthesia at a partial pressure of 35–40 atm. As we shall see, certain simple concepts of the mode of action of these lipid soluble anesthetics prove to have considerable utility in predicting the physiological outcome of breathing increased partial pressures of inert gases.

Hildebrand and co-workers suggested that helium, which is much less soluble than nitrogen, should be a superior inert gas for diving (8). Experimental chamber dives to as deep as 600 m have subsequently been made without signs of inert gas narcosis. However, a new phenomenon, characterized by trembling of the extremities, excitability and certain EEG changes, has been discovered and called the high pressure neurological syndrome (HPNS) (2). This syndrome can be relieved somewhat by slow compression rates but these themselves impose a limitation on diving practice. The HPNS appears to be a function of the elevated pressure per se and not related to inert gas narcosis since addition of nitrogen to the $He-O_2$ mixture to form a trimix ameliorates the HPNS (2). The ultimate physiological limit to deep diving thus lies beyond 60 atm and remains to be defined.

In order to consider further what limitations pressure per se may impose it is necessary to consider work on animals. The classical work of Regnard, Ebecke, Cattell and others has been reviewed recently by Fenn (5). Aquatic animals show a general stimulation of the central nervous system at pressures around 50 atm. At 200–300 atm paralysis results from spontaneous muscle contraction, while higher pressures still (400–600 atm) prove lethal. Work on amphibia enables the effect of hydrostatic and gas pressure to be compared. Newts compressed hydraulically showed slight paralysis at 140 atm and complete paralysis at 200 atm. In helium and neon paralysis occurred at similar, but slightly elevated, pressures, while in hydrogen only slight paralysis was observed at 200 atm. The protection afforded against the onset of paralysis by these gases and other anesthetics (14) has not been explained. In general then helium and neon exert effects comparable to hydrostatic pressure and neither gas appears to give rise to general anesthesia in the range of mechanically tolerable pressures,

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[1] From Session II, **Physiological Responses to the Environment**, of the FASEB Conference on *Organismal Response to the Environment* presented at the 60th Annual Meeting of the Federation of American Societies for Experimental Biology, Anaheim, CA, April 13, 1976.

[2] Pressures are given in standard atmospheres (1.03 $kg \cdot cm^{-2}$). 10 meters depth of sea water is roughly equivalent to one atmosphere.

HPNS is high pressure neurological syndrome.

although the next rare gas, argon, is an anesthetic at 20 atm partial pressure.

The physicochemical changes produced in these pressure ranges are in general not great. Equilibriums and reaction rates will be affected by about a factor of 2 or so at 100 atm, but by 1 to 2 orders of magnitude at the ocean's deepest depths (~1,100 atm), processes involving a volume increase being opposed by pressure (16). One might predict then that in the physiological pressure range (say <300 atm) only those processes in which greater than normal volume changes occur, or in which fairly critical temporal integration takes place, would be influenced significantly by pressure. A recent example of the latter type may be the pressure-induced bradycardia observed in isolated mouse sinus nodes (21). The spontaneous contraction of muscle is associated with an unusually high volume change of 350 ml/mole (6), which may be related to the observation of high pressure paralysis.

Detailed studies with mammals have been carried out over a smaller pressure range than those with aquatic animals. Although pressures as high as 300 atm have been obtained briefly, the animals are generally in poor condition above 200 atm even when the other environmental stresses, such as temperature, are controlled. When mice are compressed in an $He-O_2$ atmosphere a series of responses are observed. First, an uncoordinated trembling of the limbs and jerky voluntary movements are observed with onset pressures of 25–60 atm, depending on the compression rate. Second, convulsions, both clonic and clonic-tonic, occur at higher pressures than do the tremors. The threshold pressure for onset of convulsions may be elevated by adding an anesthetic gas to the $He-O_2$ mixture. Mouth breathing is observed at about 90 atm, but this appears to be unrelated to gas density since it occurs at the same pressure in neon–oxygen mixtures which are 5 times as dense. Finally the mice die at about 140 atm, but this event may be postponed by using slower compression rates or, more effectively, by adding anesthetic gases to the breathing mixture (3, 14). Several elegant studies, in which mice totally immersed in a highly oxygenated fluorocarbon liquid were compressed hydraulically, have demonstrated that these effects are mediated by pressure per se and are not to be attributed to helium (13).

The use of anesthetic gases to ameliorate the effects of pressure reintroduces the problem of inert gas narcosis into deep diving. However this problem is mitigated by the remarkable observation that pressure reverses the effects of anesthetics (9, 10, 14). This raises the possibility that the high pressure neurological syndrome may be controlled using trimix (e.g., He, N_2, O_2) without incurring inert gas narcosis (19). The symmetry of the situation is summarized in Table 1, where data for the elevation of convulsion threshold by addition of nitrogen and for the depression of anesthetic potency by addition of helium are presented. At present the most successful approach for assessing the role of inert gases in modifying the effects of pressure per se is the approach based on simple physicochemical concepts developed to explain the mechanism of action of anesthetic agents. These concepts enable quantitative predictions to be made of the optimum balance in the trade-off between inert gas narcosis and the HPNS. They also provide a conceptual link between the molecular level interaction of the anesthetics with their site of action in a membrane and the behavior of the whole animal. Thus anesthetic potency correlates remarkably well with lipid solubility. However the pressure reversal of anesthesia suggests that the anesthetics not only dissolve in, but also expand and fluidize, the lipid bilayer regions of biomembranes (10, 20). Anesthetics have in fact been observed to fluidize membranes (17, 23) and this fluidization is reversed by pressures of the same magnitude as those observed physiologically (23). Anesthetic-induced membrane expansion has also been measured and found to be consistent with that required for anesthesia (22). If an increase of membrane volume or fluidity can lead to anesthesia, then it seems probable that a corresponding decrease may also result in marked changes in membrane function such as the excitability associated with the high pressure neurological syndrome (HPNS). The mechanism by which these changes in fluidity of the lipid bilayer could give rise to such profound events as anesthesia and the HPNS remains to be clarified. Certainly the changes induced in the lipid bilayers themselves are small, but the emerging relationship between lipid fluidity and the function of membrane protein suggests plausible mechanisms. Electrophysiological studies may provide further insight (4, 7, 11).

TABLE 1. Partial pressure of nitrogen to cause anesthesia or prevent hyperbaric convulsions in mice at various pressures

	Nitrogen partial pressure at	
Total pressure	Anesthesia	Convulsions
39	38	—
69	44	0
98	46	9.4
110	48	17
119	49	32

Pressures in atmospheres. Anesthesia data (Wilson and Miller, unpublished). Convulsion data ref 3. Gas mixtures contain 1 atm O_2. The balance is helium.

We shall now consider the formulation, testing, and application of the critical volume hypothesis, which may be stated in two forms. First, anesthesia occurs when the volume of a hydrophobic region is caused to expand beyond a certain critical volume by absorption of an inert substance. An applied pressure opposes this expansion and reverses the anesthesia. Second, convulsions occur when some hydrophobic region has been compressed beyond a certain critical amount by the application of pressure. Absorption of an inert gas will compensate for such compression and raise the convulsion threshold pressure.

These hypotheses can be tested against data of the type given in Table 1. To calculate the expansion caused by an anesthetic when it dissolves in a hydrophobic fluid it is necessary to know the solubility in the membrane involved. Unfortunately few such data are available and in any event the exact site of action, and hence the appropriate membrane composition, is unknown. Because of this a number of model solvents have been used; olive oil, benzene, and carbon disulfide provide particularly good analogs and the conclusions derived turn out not to be particularly solvent dependent. It is also possible to test the hypotheses algebraically without assuming a model solvent (20). This becomes very cum-

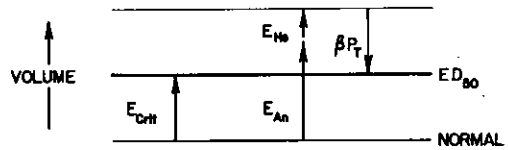
bersome however, especially at higher pressures where a number of corrections for nonideality must be made. In this paper the calculations are illustrated using benzene as the model because the required physical parameters have been most accurately determined for this solvent.

The required equations are set down in Fig. 1. The gross fractional expansion caused by dissolving a gas is calculated from a knowledge of the partial molar volume of the gas in the solvent. The mechanical compression resulting from elevating the partial pressure is given by the compressibility. Two corrections need to be taken into account: one for deviation of the gas mixture from ideality and the other resulting from the reduction in solubility of the gases at high pressure (deviations from Henry's law) (20). With typical diving gases these corrections reduce the calculated expansion by 10–20% at 100 atm. (This is not sufficient in itself to account for pressure reversal.) In a dissolved gas mixture the total gross expansion is given by the sum of the individual terms. For a given physiological end point, which may be achieved at different pressures according to the gas mixture employed (e.g., Table 1), the total gross expansion may be calculated. Plotting this versus the total pressure should yield a straight line whose slope is the compressibility and whose intercept is the critical volume change as illustrated in Fig. 2. In Fig. 3 data for iso-anesthetic and iso-convulsive end points are tested in this way. The fit is acceptable, a volume change of around 1% leads to anesthesia (expansion) or convulsions (compression), and the site of action of convulsions is 4–5 times as compressible as the anesthetic site (18). The degree of agreement is remarkable for such a simple model.

Although a number of uncertainties surround the conclusions these are probably not serious. Thus the convulsion threshold depends on the strain of mice—an A/J strain in this case which convulses at a lower pressure than the CD strain used for the anesthesia work. The limited data on convulsions in CD mice suggest they exhibit a lower compressibility and a lower critical volume than A/J mice (K. W. Miller, unpublished calculations). In either case, however, the site of action of convulsions is distinct from that for anesthesia. Furthermore no model as simplistic as the critical volume hypothesis can be expected to account for the neurological accommodation or adaptation implied by the compression rate dependence of the convulsion threshold. However the data used here were all obtained with a uniform compression rate of 40 atm/hr and the convulsion thresholds differ from this by no more than 20% at higher and lower rates.

Another shortcoming of the model follows from the conclusion that there are distinct sites of action mediating the anesthetic and convulsant sites. This conclusion can also be reached algebraically without assuming a particular solvent model (K. W. Miller, unpublished calculations). However, in the model calculations the gas solubilities of these two sites have been assumed to be identical so that the difference must perforce appear entirely in the compressibilities. These problems reflect our ignorance. No black-box approach such as this can be expected to do more than provide a self-consistent description and verify in a general way the underlying concepts. The high degree of consistency of the model, however, is challenging and points the way to more detailed biophysical investigations which alone can provide a direct test of the underlying assumptions.

The critical volume hypothesis can now be used to predict the composition of gas mixtures required to avoid both anesthesia and convulsions. It may be seen immediately that no single mixture can prevent a volume change at both sites, and this is bound to impose a limiting pressure beyond which both end points cannot be avoided simultane-



$$E_{Crit} = (E_{He} + E_{An}) - \beta P_T$$

$$(E_{He} + E_{An}) = \beta P_T + E_{Crit}$$

Figure 2. Equations for testing the critical volume hypothesis for anesthetic action. E_{crit} is the critical expansion which results in anesthesia in half of a group of animals (ED_{50}). E_{An} is the expansion caused by the dissolved anesthetic at a concentration greater than its ED_{50}. E_{He} is the expansion caused by helium dissolved at a pressure that reverses anesthesia. β is the compressibility and P_T the total mechanical pressure.

Figure 1. The net expansion, E, occurring when a gas dissolves in a fluid is given in the upper equation for the second component of a gas mixture. $\bar{V}$ is the partial molar volume of the gas dissolved in the fluid of molar volume V_m; x is its mole fraction solubility at a partial pressure of 1 atm, and P is the partial pressure of the gas. β is the compressibility of the solvent. Two correction terms must be applied to the first term on the right, and these are given. P^* is the fugacity of a gas at partial pressure P_i in a mixture of two gases, X_1 and X_2 are the mole fractions of the gases in the mixture, and B the second virial coefficient. The second correction is for deviations from Henry's law. C is the mole fraction concentration at partial pressure P. P_T is the total pressure, R the gas constant and T the absolute temperature. For further details see (20).

CRITICAL VOLUME HYPOTHESIS

Net Expansion – each gas

$$E_2 = \frac{\bar{V}_2 \cdot x_2 \cdot P_2}{V_m} - \beta \cdot P_2$$

Correction terms

(1) Gas imperfections

$$\ln\left(\frac{P^*}{P_i}\right) = \frac{1}{RT}\int_0^{P_T}\left[x_1 \cdot B_{11} + x_2 \cdot B_{12}\right] dP$$

(2) Dependence of solubility on pressure

$$\frac{d\,(\ln(c/P))}{dP_T} = -\frac{\bar{V}_2}{RT}$$

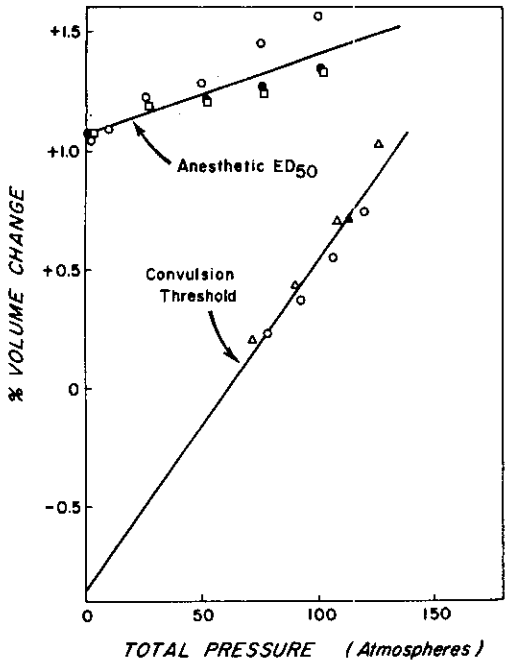


Figure 3. Tᵉ ercent volume change calculated for the gas mixtures (e.g., $E_{He} + E_{An}$) that give rise to an anesthetic ED_{50} or a convulsion at the total pressure P_T. ○ He–N_2O; △ He–N_2; □ Ne–N_2O; ● H_2N_2O; ▲ H_2 alone. For data sources see (18). Reproduced with permission from reference (18). Copyright 1974 by the American Association for the Advancement of Science.

ously. In addition since anesthetics and pressure are both nonspecific in action it seems probable that there is a spectrum of similar sites some of which might be involved with control of vital cardiac and ventilatory processes. The roles of these in limiting the physiologically tolerable pressures are unknown. Furthermore there are unrelated mechanisms where pressure or anesthetics may act either independently of each other or, more seriously, even synergistically. Such an effect has been reported, for example, on the slowing of the rate of beating of the pleopods of *Marinogammarus marinus* (12) by 0.005 atm of halothane ($CF_3CHClBr$), which is enhanced by application of 136 atm, a pressure which in the absence of anesthetic has no effect.

In spite of these possible limitations the mixtures predicted by the critical volume hypothesis appear realistic in so far as they have been tested. Thus if one calculates the net volume change that occurs when compression is carried out hydraulically, or with a number of inert gases, the correct ranking order of convulsion thresholds is obtained. Nitrogen is found not to cause convulsions because its solubility is high enough to result in net expansion, while with helium and neon net contraction occurs mainly because of their low solubility (Fig. 4). The result of mixing a strongly expanding gas, such as N_2O, with helium is to reduce the net compression. The mixtures corresponding to expansion sufficient to cause anesthesia or compression sufficient to cause convulsions are summarized in Fig. 5. Here the optimum mixture for the point where the anesthesia and convulsion thresholds converge is seen to contain a little over 1% N_2O. Beyond this pressure it is necessary to provide deeper and deeper anesthesia to prevent convulsions. We have recently confirmed the latter prediction in our laboratory. With CD mice it is possible to prevent convulsions elicited by sound without loss of righting reflex at 130 atm total pressure, but at 200 atm complete loss of righting reflexes occurs before

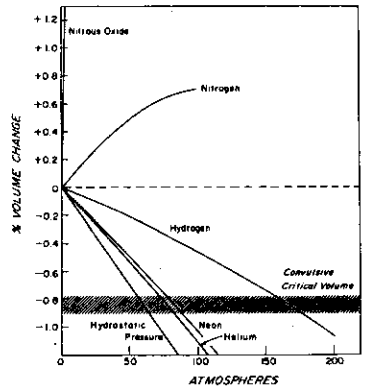
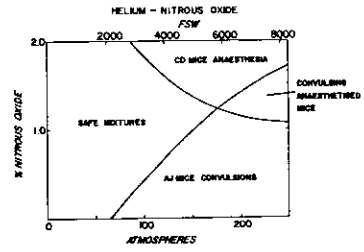


Figure 4. The net volume change (e.g., $E_{He} - \beta P_T$) calculated for the site of action of convulsions using the compressibility and critical volume derived from Fig. 3. The shaded area indicates the critical contraction at which convulsions first occur.

these convulsions can be prevented. One thus achieves the state of a convulsing anesthetized mouse, which confirms the prediction that the two sites of action are indeed separate! Because of the phenomenon of accommodation to pressure, Fig. 4 does not define the ultimate pressure limits. However even with cautious compression schedules the condition of mice at pressures above 200 atm is rarely good. Further extension of pressure tolerance cannot then be achieved with gas mixtures. We do find that agents such as phenobarbital have some advantages, but more specific pharmacological intervention will be required to significantly raise the tolerable threshold further. Whether it will be possible to breed animals with tolerance to pressure remains to be seen.

It is possible to extend this analysis to include predictions for manned

Figure 5. The total pressure at which anesthesia or convulsions will be observed calculated as a function of percentage of nitrous oxide mixed with helium. FSW, feet of sea water.



diving. Here the acceptable gas mixtures are bounded by the inert gas narcosis and tremor thresholds. These are considerably more subjective phenomenons than convulsions and general anesthesia and consequently there are less reliable objective data available. Sufficient accounts of nitrogen narcosis in mixtures of helium and nitrogen have been given to allow one to calculate that the compressibility at this site of action does not differ significantly from that for anesthesia in mice, although of course the critical volume is much smaller. It is thus possible to estimate that a mixture of 10% nitrogen and 90% helium should not cause significant narcosis at any pressure (K. W. Miller and M. Wilson, unpublished calculations). How far the percentage of nitrogen needs to be raised to avoid significant hyperexcitability is not yet clear; nor are any systematic data available for testing the theory. However, the use of 5–10% nitrogen in helium does appear to improve performance following rapid compression to depths of about 300 m (2).

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British Journal of Pharmacology and Chemotherapy, March, 1967, vol. 29, No. 3, pp. 350-366.

EXPERIMENTS ON THE CONVULSANT AND ANAESTHETIC EFFECTS OF OXYGEN

W.D.M. Paton

SUMMARY

1. The sensitivity of mice and rats to oxygen has been measured by determining the time to produce convulsions at various oxygen tensions. The observation by Marks that the logarithm of the convulsion time is distributed normally has been confirmed. Rats are generally less sensitive than mice, and much less variable.

2. As the oxygen tension is raised, the convulsion time shortens, until a minimum convulsion time of 3-4 min for mice and about 6 min for rats is reached at about 100 p.s.i.g. Above this tension, the convulsion time is not reduced further. There is also a minimum tension below which convulsions cannot be produced, so that the pressure-convulsion time relation takes a hyperbolic form.

3. The earlier a convulsion occurs, the higher the lethal effect of oxygen.

4. At very high tensions (150 p.s.i.g.) the convulsion produced by oxygen is very brief and is followed by a state resembling anaesthesia. If the animal is pretreated with bromide in a dose insufficient to produce behavioural changes, and then exposed to high oxygen tensions, the convulsion is abolished and the animal passes directly and rapidly into this anaesthetized state. It is suggested that this represents a true anaesthetic action of oxygen, comparable with that of the inert gases; the fat solubility of oxygen, approximately twice that of nitrogen, is compatible with this suggestion.

5. Significant prolongations of convulsion time of mice in oxygen at 65 p.s.i.g. were obtained with sodium bromide, diethazine, chlorpromazine, paramethadione and trimethadione, and mephenesin. Cobalt acetate, hexamethonium, dimercaprol, procaine amide and morphone were ineffective. Diethazine was also shown to be effective in rats. Preliminary evidence was obtained that methyl fluoroacetate potentiated oxygen convulsions in rats.

6. It is suggested, in the light of these results, that oxygen, in producing convulsions, acts not directly but by poisoning some enzyme system, so leading to accumulation of a convulsant substrate or depletion of a depressant product; and that the site of initiation of convulsions is subcortical.

U. S. NAVAL MEDICAL BULLETIN

VOL. XXXV OCTOBER 1937 No. 4

SPECIAL ARTICLES

QUANTITATIVE STUDY OF MENTAL AND NEURO-MUSCULAR REACTIONS AS INFLUENCED BY INCREASED AIR PRESSURE[1]

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Men exposed to increased air pressures of 5 atmospheres (gage) or above have a definite feeling of stimulation and well-being which they liken to a feeling of "drunkenness." During such an air-pressure exposure, they have an exaggerated confidence in their ability to accomplish a given task, but to the observer their actual accomplishment falls far short of that demonstrated at atmospheric pressure. This failure of accomplishment was noted, associated with emotional disturbances, in the 1931 deep-diving trials of the British Navy, and was reported by both Phillips (1), and Hill and Phillips (2). Behnke, Thomson, and Motley (3) wrote a theoretical paper entitled "The Psychologic Effects from Breathing Air at 4 Atmospheres Pressure" in which they described the abnormal reactions of nine individuals engaged in physiological research work under pressure of 4 atmospheres (absolute). Damant (4) also made reference to the change in behavior which men undergo when exposed to increased air pressure. Although much has been written concerning the impaired neuromuscular coordination, the slowed mental activity, and the alterations of behavior brought on by exposure to increased air pressure, no one has reported any quantitative experiments designed to actually demonstrate the type and degree of these changes. The present paper is a report of such a quantitative study.

Problems.—Sets of simple problems, each sheet of which consisted of four problems—namely, one each in addition, multiplication, subtraction, and division—were compiled. One of the set was used for each pressure studied, the first sheet of the set being used at atmos-

[1] Received for publication May 4, 1936. From the laboratory of the experimental diving unit, Department of Construction and Repair, Navy Yard, Washington, D. C.

[2] We wish to express our appreciation for the suggestions and advice given by Commander E. L. Gayhart, Construction Corps, U. S. Navy, and Commander F. S. Johnson, Medical Corps, U. S. Navy, members of the advisory committee; J. A. Hawkins, D. Sc., and Lt. (Jr. Gr.) O. D. Yarbrough, Medical Corps, U. S. Navy, members of the staff; Lt. J. A. Hollowell, U. S. Navy, officer in charge, and Lt. R. A. Hansen, U. S. Navy, formerly officer in charge of the experimental diving unit.

pheric pressure immediately before the air-pressure dive, and the second sheet being used at the pressure selected. The difference of time in seconds (stop watch) required to complete each sheet of problems was recorded. The difference in the number of errors at atmospheric pressure and at each increased air pressure was also recorded.

Number cross-out.—In using the number cross-out sheets, the subjects were asked to cross out as many of a given numeral as possible in 1 minute. Two test sheets were run immediately before each pressure, and one at the pressure being studied.

Light-to-touch reaction time.—The subject sat in the recompression chamber described by Hawkins and Shilling (5), and watched an electric-light bulb situated in an eye port. When the light was turned on, the subject pressed a telegraph key. A Fauth chronograph with three solenoid operated pens was used to record the operations; one pen was operated by a chronometer and made a mark every half second on the cross-section paper covering the drum, the second pen made a mark each time the light in the eye port was turned on, and the third pen made a mark when the subject within the chamber pressed the telegraph key. The light was turned on and off at irregular intervals during a 2-minute run, and the lag in response as measured by the distance between the two pen marks was recorded as the reaction time. All of the 40 to 50 responses for the 2-minute run were measured and the average taken as the figure for the run. Control runs were made at atmospheric pressure before each pressure run.

SUBJECTS

The 46 subjects for these tests were the officers and men attached to both the experimental diving unit and the Deep Sea Diving School, and the last two classes of students at the Deep Sea Diving School.

Experimental data.—The difference in the time required (measured in seconds) to complete a sheet of problems at atmospheric pressure, and the time required to complete the paired sheet of the set under increased air pressure is reported in table 1. The first column presents the results of an atmospheric check run. In this run, the first sheet of each set was run at atmospheric pressure as usual, but the second sheet of each set instead of being run under increased air pressure was also run at atmospheric pressure. The very small time variation (0.35 second) is proof that there is not sufficient difference in the problem sheets to account for the increases in time required for accomplishment under increased air-pressure conditions. It will be noted that the additional time required at 90 feet is greater than that required at 100 feet (44.5 pounds gage air pressure). This is un-

doubtedly due to the fact that for many subjects this 90-foot air-pressure dive was their first pressure experience, and an additional element of apprehension was added to the real effect of the increased air pressure. The progress from 100 feet to 300 feet is marked by steadily increasing time differences required for completing the problems, and this increase in time difference is the result of the increased air-pressure effect. At 300 feet, the increase in time is 31.42 seconds, which is an increase of 52.8 percent over the atmospheric check run in which the arithmetic mean for the actual time of accomplishment, for all problem sheets, was 59.54 seconds with a standard deviation of 21.55.

TABLE 1.—*Additional time required to work problems under pressure*

Pressure, feet (gage)	0	90	100	125	150	175	200	225	250	275	300
Arithmetic mean (sec.)	0.35	11.09	6.89	7.65	9.74	11.95	13.98	17.17	26.07	26.53	31.42
Standard deviation	3.25	15.35	11.85	9.54	12.05	16.25	14.4	14.65	25.65	31.45	34.85

As additional evidence of the actual slowing effect on the mental processes even of experienced divers, the staffs of the experimental diving unit and the Deep Sea Diving School, were tabulated separately, and the data presented in table 2 were obtained. Here, again, we find that there is an actual slowing due to the effect of increased air pressure; although in this experienced group the slowing is noticeably less.

TABLE 2.—*Additional time required to work problems under pressure, experienced group only*

Pressure, feet (gage)	0	90	100	125	150	175	200	225	250	275	300
Arithmetic mean (sec.)	1.64	2.55	3.42	3.91	4.66	8.00	11.75	15.73	16.33	17.09	24.36
Standard deviation	3.05	5.82	7.85	7.30	7.99	8.75	14.30	14.65	10.45	10.60	21.10

The errors made on both the atmospheric control sheet and the pressure sheet were noted, and the difference recorded as due to the increased air-pressure effect. These data are presented in table 3, and demonstrate that there is an adverse effect on the accuracy of the group in working problems under increased air pressure. The arithmetic means do not seem large, but when it is realized that there are only 19 possible errors, it will be seen that an average increase in errors of 3.02 for each individual at 300 feet is noteworthy. Actually, several of the subjects went to pieces so completely as to make

10, 11, or 12 errors under pressure, and one or two failed completely to be able to finish so simple a task as the problems.

TABLE 3.—*Additional errors in working problems under pressure*

Pressure, feet (gage)	0	90	100	125	150	175	200	225	250	275	300
Arithmetic mean	0.18	0.85	0.49	0.42	0.72	0.84	1.22	0.88	2.18	2.66	3.02
Standard deviation	.71	2.29	6.20	1.40	1.17	1.25	2.06	1.33	1.88	3.08	2.92

Number cross-out.—The results obtained from the number cross-out sheets are presented in tables 4 and 5. Table 4 shows the difference in the number of a given numeral crossed out; each pressure compared with its corresponding atmospheric pressure run. The arithmetic means, representing a decrease in the number of the given numeral crossed out, are not large; however the loss progresses steadily as the pressure increases. Since the test is based almost entirely upon attention and neuromuscular control and requires no memory or reasoning this loss in ability is significant. Of even greater significance is the increase in errors, shown in table 5, which occurred while doing the number cross-out test. At 300 feet there is an average of 2.62 errors per individual in this simple test.

TABLE 4.—*Decrease in number of numerals crossed out under pressure*

Pressure, feet (gage)	90	100	125	150	175	200	225	250	275	300
Arithmetic mean	−.59	−.09	−2.26	−2.30	−2.49	−2.55	−4.24	−5.85	−6.43	−8.74
Standard deviation	3.87	5.65	4.01	3.55	5.04	5.34	4.34	5.44	3.99	5.46

TABLE 5.—*Additional errors in working cross-out test under pressure*

Pressure, feet (gage)	90	100	125	150	175	200	225	250	275	300
Arithmetic mean	1.47	0.74	1.62	1.70	1.72	1.83	1.90	2.22	2.30	2.62
Standard deviation	1.76	1.77	2.04	2.14	3.49	2.61	2.15	3.92	2.73	3.22

Light-to-touch reaction time.—Table 6 presents the results of this experiment, and here, again, a slight but definite slowing of reaction time under increased air-pressure conditions is shown.

Additional experiments were conducted at various pressures in "marble sorting", "questions of common sense", and "right and wrong words" which showed the same tendency to loss of ability under increased air pressure, but these experiments were not well adapted for repeated use and were therefore dropped.

TABLE 6.—*Light-to-touch reaction time (seconds)*

Subjects	Pressure, feet (gage)							
	0	150	0	200	0	250	0	300
A	0.219	0.248	0.201	0.216	0.209	0.247	0.204	0.232
B	.220	.237	.210	.221	.216	.222	-------	-------
C	.235	.253	.229	.211	.164	.230	.215	.242
D	.260	.245	.183	.264	.263	.246	.183	.280
E	.202	.218	.218	.243	.224	.240	.246	.261
F	.211	.253	.227	.248	.193	.237	.210	.235
G	.203	.204	.189	.213	.209	.235	-------	-------
H	.174	.206	.206	.218	.214	.222	-------	-------
I	.162	.234	.214	.238	.231	.244	.200	.241
J	.232	.236	.190	.250	.242	.260	.200	.258
K	.252	.265	.256	.299	.240	.316	.216	.303
L	.251	.240	.214	.246	.195	.233	-------	-------
M	.221	.252	.229	.281	-------	-------	-------	-------
N	.166	.224	.208	.258	.232	.293	-------	-------
Average	.215	.237	.213	.242	.218	.248	.209	.257

Special case.—As an example of the effect of increased air pressure on one individual, the following case is reported:

Date: October 23, 1935.

Pressure: 275 feet; suit dive.

Condition previous 24 hours: Normal except for loss of sleep due to 2 a. m. to 6 a. m. watch. The physical examination revealed no defects, and the Schneider score was 13.

Mental tests (275-foot preliminary air run): "Problems", an increase of 24 seconds and 11 errors over the paired atmospheric run. "Number cross-out", a decrease of four numerals crossed out and an increase of four errors over the paired atmospheric run.

Required suit dive task: Remove nut from spill pipe attached to iron work bench, hand nut to diving partner, take hose from partner, attach hose to spill pipe, tighten loose fitting with wrench, open spill pipe valve, close spill pipe valve, take hose off, put nut on, and tighten nut with wrench. Subject started task as usual without being told, but dropped the nut after removing it; he picked it up (should have let partner do this), and put it on the pipe instead of putting on the hose. Next, he opened the spill pipe valve as if the hose had been attached, but did not close the valve. Then he took the wrench and tightened the nut as if the job was completed.

The instructor told him to repeat the job, and he responded, "Stand by to come up." As further instructions failed to elicit any response, his partner was asked to take his turn on the same job. His partner removed the nut and tried to hand it to him, but he would not take it, so his partner placed the nut on the work bench. Instead of handing his partner the hose, as he should have done, he tied the hose around the spill pipe.

At this point it seemed wise to terminate the run and reduce the pressure. The instructors kept in communication with him during the decompression, but at 120 feet he suddenly left his tank air-control valve and picked up the nut from the bench and started to put it back on the pipe. They did not succeed in getting him back to his valve until the first stop (110 feet) in the decompression had been reached. In response to phoned questions during the remaining decompression, he repeatedly stated he was all right and that he had completed his job correctly.

Upon reaching the surface and being questioned, he at first stated he had attached the hose and completed the job; but upon further questioning he admitted he could only remember the following incidents: Taking off the nut, turning on the valve, seeing his partner with him by the workbench, and being told to stand by to come up. He has no memory of the other happenings until he saw the nut on the workbench. He not only knew that he should not pick up the nut when he was doing the job but he also knew it should be on the pipe for a finished job; consequently this started a debate in his mind that seemed to last for a long time, and to be a thing apart from him. He further stated, "These two ideas were coming from two directions like, and they seemed to bounce back and forth in my mind until the idea to pick up the nut became so strong I had to do it, and so I made a dive for it and put it on." At this point, although he thought he was still on the bottom, he was actually at 120 feet. He said that during the dive he knew vaguely that something was wrong, but could not tell what, and cannot now explain. However, when his partner, at the 110-foot stop, punched him in order to get him back to his valve and away from the nut, "everything became clear and plain, like something had been rubbed out."

The problem sheets worked by this subject at both atmospheric pressure and at 275 feet (gage) air pressure demonstrated errors in the air-pressure dive that paralleled the failure of task accomplishment in the actual suit dive. Also, both of these failures under increased air pressure are undoubtedly related to the rather low normal mental ability of this subject.

The problem sheets presented for this subject also show a lack of neatness under pressure, which is common to all subjects. The figures made under pressure are often almost unintelligible, whereas at atmospheric pressure the same subject writes very clearly and neatly.

During the progress of the last 3 years' work at the experimental diving unit and the Deep Sea Diving School there have been a number of occasions in which peculiar emotional reactions have been observed, as well as other cases of failure of accomplishment similar to the example cited. However, these cannot be quantitatively evaluated, and therefore are not included in this report. All those experienced in diving know that during exposure to high pressures there is an appreciable dulling of mental ability, characterized by increased difficulty in the assimilation of facts and in the making of quick and accurate decisions. This dulling may be summed up as a slowing of the process of cerebration. Also, there is a lengthening of the reaction time and a loss in neuromuscular control and response. The data presented in this report serve to demonstrate the accuracy of these experiential deductions and to measure them quantitatively.

In addition, personal experience and careful observation of many men taking pressure has led to the formation of two conclusions, namely, that increased experience materially lessens the subjective

effect of pressure, and that there is a definite relation between normal "atmospheric pressure" mental ability and failure of accomplishment under increased air pressure. That is, men with high mental ability do not fail as quickly under pressure as do those with low mental ability. Further study of this relationship must be conducted; however, even now there is an indication that tests can be devised which could be successfully used in the selection of men who will be fitted for deep-sea diving.

The cause of this slowing has been variously attributed: To the stimulating effect of the increased tension of oxygen, to the narcotic effect of the increased tension of nitrogen, to the pressure effect alone, and to a purely psychological—not physiological—effect. Many of the earlier authors believed the increased partial pressure of oxygen to be the factor that influences the physiological changes produced by exposure to compressed air; furthermore Damant (4) suggested that the psychological changes might also be thus explained. In support of this oxygen theory, it may be pointed out that most authors believe that the decreased partial pressure of oxygen is the factor that causes both the physiological and psychological changes encountered in altitude work.

Both Phillips (1) and Hill and Phillips (2) state that the psychological changes encountered in deep diving are due to purely mental—not physical—causes. They described several cases of failure of accomplishment under pressure which they demonstrated by psychoanalysis to be due to claustrophobia. The data presented in the present report definitely demonstrates that there is a marked change in response, produced by increased air pressure, that cannot be considered to be caused by a purely mental reaction such as claustrophobia.

Behnke, Thomson, and Motley (3) attribute these psychological changes entirely to the narcotic effect of the increased nitrogen tension. Against this theory is the fact that the greatest change is noticeable immediately upon reaching the pressure and lessens as the subject becomes adjusted. It is well known that if pressure is applied too quickly the diver becomes dizzy and often is so dazed as to require several minutes to orient himself. Consequently, if the cause were nitrogen narcosis, the difficulty would increase with exposure rather than decrease. Also, against this theory is the fact that as the nitrogen tension increases, the oxygen tension also increases proportionately and would, therefore, tend to counteract the narcotic effect of the nitrogen.

The true cause of the slowed mental and neuromuscular activity encountered in high pressure air work has not been satisfactorily demonstrated. It may be a combination of all of the above-mentioned

factors, or it may, in some way, be due entirely to the effect of the pressure itself. Work is in progress at the experimental diving unit which, it is hoped, will shed additional light on the true cause of the mental and neuromuscular changes produced by exposure to increased air pressure.

SUMMARY

Data which included problems, number cross-out tests, and light-to-touch reaction time worked at both atmospheric pressure and under increased air pressures, have been presented.

These data give quantitative evidence of the slowing effect that increased air pressure has upon the normal mental and neuromuscular responses.

Experience in work under pressure tends to lessen this effect, and low mental ability undoubtedly enhances early and extreme failure under high air pressure.

The cause of this effect was discussed.

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ABSTRACT

Stern, S.A. and H. L. Frisch

Dependence of inert gas narcosis on lipid "free volume."

J. Appl. Physiol. 34:366-373. Mar. 1973.

This paper suggests that the anesthetic (or narcotic) potency of metabolically inert gases is due to their effect on the "free volume" of a bulk lipid phase, possibly in the cell membrane. According to this hypothesis, narcosis occurs when the inert gas dissolved in the lipid phase causes the free volume to exceed a specific threshold value. The anesthetic potency of a gas depends not only on its lipid solubility as postulated by the Meyer-Overton hypothesis, but also on the thermal expansivity, and compressibility of the lipid phase as well as the environmental temperature and hydrostatic pressure. The new hypothesis is expressed in quantitative terms and shown to be in good agreement with experimental data from the literature for both pure gases and gas mixtures. In particular, the theory offers an explanation for the reported pressure reversal of inert gas narcosis and predicts that it should be possible to reverse this type of narcosis also by a change of temperature. Experimental approaches for further testing of the free-volume hypothesis are outlined. (Aubhots' abstract)

Anesthesiology 18:97-105. 1957.

CORRELATION OF van der WAALS CONSTANTS WITH ANESTHETIC POTENCY.

R. J. Wulf and R. M. Featherstone

SUMMARY

Definite correlations between anesthetic potency or non-potency of a series of atoms and molecules and their van der Waals physical chemical constants have been shown. These observations indicate that the attributes of many molecules which are important in bringing about "anesthesia" may be well expressed by the concept of "approximation to ideality." This concept has been given substance through the development of an equation by van der Waals, which contains correction terms for the major deviations from ideality. The increasing potency of clinical anesthetic agents has been shown to parallel in general the increasing magnitude of these constants. The inert gas xenon has been shown to possess physical chemical properties which can be used to explain its classification with nitrous oxide and ethylene as an anesthetic agent.