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OF THE

UNDERWATER PHYSIOLOGY

SYMPOSIUM

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ABSTRACT

These proceedings represent a compilation of those papers presented at a Symposium on Underwater Physiology, January 10-11, 1955, sponsored by the Office of Naval Research and the Panel on Underwater Swimmers of the National Academy of Sciences-National Research Council Committee on Undersea Warfare.

The range of interests covered includes oxygen toxicity, decompression and bends, and respiratory problems, with special emphasis on their implications in underwater swimming. Some of the earlier work in these areas of interest has been re-examined in the light of current problems.

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FOREWORD

Recorded here are the proceedings of a symposium on Underwater Physiology held at the New State Department Building, Washington, D. C., January 10-11, 1955, under the sponsorship of the Panel on Underwater Swimmers of the Committee on Undersea Warfare and the Office of Naval Research. The phases of underwater physiology considered at this symposium apply to all human underwater activities, but the emphasis has been placed on the special conditions met in the use of self-contained underwater breathing apparatus.

The general problems associated with deep-sea diving also apply to the self-contained diver or underwater swimmer. In addition there are numerous other problems peculiar to this activity as a result of a completely different type of breathing equipment, lack of constant attention and supervision from the surface and the missions performed.

Beginning with the advent of the underwater swimmer as an effective military unit during World War II, the applications of this skill to both civilian and military situations have increased at such a rate that neither the technology nor the basic scientific data have kept abreast of the needs in this field of activity.

The Panel on Underwater Swimmers of the Committee on Undersea Warfare and the Office of Naval Research agreed to sponsor jointly a symposium on underwater physiology with the following objectives:

a. to summarize what is currently known in the field of physiology as applied to underwater environment;

b. to direct the attention of those working in physiology to the various problems which exist;

c. to encourage consideration of these problems in the evaluation of related research;

d. to formulate proposals for future research and development leading to increased capabilities of underwater swimmers.

These proceedings are composed of the numerous papers presented at the meeting and the discussions which followed. While many of the papers refer to earlier work in the field of diving physiology, the basic information was reconsidered in view of the new problems which have arisen. The discussions represent a valuable re-assessment of much of this information. Included also are the basic references to the various topics considered. This reference list is not complete in that it contains only those works specifically cited by those authors whose papers were presented.

The formal presentations and discussions were supplemented by active demonstrations and displays at the U. S. Naval Experimental Diving Unit, affording an opportunity to examine some of the equipment available for use by underwater swimmers as well as to obtain first-hand information regarding special instrumentation and techniques employed in almost all phases of research in

underwater physiology.

In addition to Navy and Government representatives, the 1955 Underwater Physiology Symposium was attended by representatives from university and industrial research organizations, the Dominion of Canada, and the United Kingdom.

The Chairman of the symposium, Dr. Eugene F. DuBois, was unable to attend because of illness. Dr. C. J. Lambertsen (Chairman of the Panel on Underwater Swimmers), Captain A. R. Behnke (Radiological Defense Laboratory, San Francisco), and Dr. H. Rahn (University of Rochester) acting for Dr. DuBois, presided over the sessions on Oxygen Toxicity, Decompression and Bends, and General Respiratory Problems, respectively. The program committee consisted of Dr. Eugene F. DuBois (Cornell University Medical School), Dr. F. H. Quimby (Physiology Branch, Office of Naval Research), and Dr. C. J. Lambertsen (University of Pennsylvania). Mr. J. T. Wren of the Panel staff was responsible for the meeting arrangements. These proceedings were assembled and edited by Loyal G. Goff, Technical Assistant, Panel on Underwater Swimmers, and represent a contribution by almost everyone who attended the symposium and by the organizations which were represented. The members of the group express their appreciation to the staff of the Committee on Undersea Warfare for copy editing, production, and distribution of the final report.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1.1 GENERAL WELCOME

C. J. Lambertsen
School of Medicine
University of Pennsylvania

The Panel on Underwater Swimmers and the Physiology Branch of the Office of Naval Research welcome you to the first Symposium on Underwater Physiology. We had hoped to have Dr. Eugene DuBois present to act as chairman for the Symposium. Unfortunately he became ill and will not be able to attend. We shall all miss having the advantage of his many years of association with submarine problems and his interest in the growth of self-contained diving.

In the total effort of the Panel in the rapidly expanding military field of individual underwater operations, it is necessary to seek technical advances in underwater communication, navigation, ordnance, hydrodynamics, and photography, as well as in personnel selection and other specialized areas. The usual limiting factor, man himself, has for a considerable time presented the greatest obstacle to a major breakthrough in underwater potential. Several physiological barriers exist for man underwater. The most important of these will be discussed today. It is a significant fact to keep in mind at the outset that not one of these barriers has as yet been overcome.

Because now, as with the development of aircraft, it is easily possible to build mechanical equipment with a diving potential greater than that of its user, greatly increased attention must be given to the human aspects of diving. This is particularly true for self-contained diving and underwater swimming, where the diver carries his own supply of respiratory gases, serves as his own tender, and often is without connection to the surface.

We are fortunate in having Captain O. D. Yarbrough here to do the almost impossible job of summarizing in twenty minutes the important physiological barriers in diving. Captain Yarbrough is well known as a senior submarine medical officer, as an investigator in the field of diving physiology, and as one of the most articulate submariners who has ever schnorkeled his way through a symposium.

1.2 OUTLINE OF MAJOR PROBLEMS OF UNDERWATER SWIMMING AND SELF-CONTAINED DIVING

O. D. Yarbrough
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I am most appreciative of this opportunity to address so distinguished a conclave wherein has been assembled a hard corps cadre representing the sum total of scientific and practical knowledge, at least within these continental confines, with regard to individual underwater activity.

By way of introduction I should state that the title of this presentation according to the agenda is "An Outline of the Major Problems of Underwater Swimming and Self-Contained Diving". It is obvious that in the twenty minutes allotted such a presentation is beset with the difficulty of providing sufficient information for orientation and yet of not usurping the prerogatives of subsequent speakers.

Man's proclivity to invade those areas of environment for which he is physiologically ill adapted is well documented by the historical accounts of man's constant attempts through the centuries to penetrate, survive, and perform useful functions beneath the surface of the seas. The extensive and exhaustive efforts of the operational and scientific developmental echelons of those seeking to advance human ability to reside constructively under water have, as the diving archives reveal, gradually evolved a science that for the want of better nomenclature has become known as submarine medicine. It is evident that this title is somewhat misleading. It connotes to the uninformed a science that treats of the medical aspects of residence in submarines. Underwater medicine would perhaps be more explicit, in that the true implication of encompassing the medical aspects of all human underwater activity is revealed.

All individual underwater activity can be divided, with some reservations, into two categories, namely, deep-sea diving and shallow-water diving. The former category, deep-sea diving, is usually defined as that type of underwater operation that exceeds 100 feet in depth, performed in more or less open sea remote from land by means of the conventional deep-sea diving equipment. In contrast, shallow-water diving is a rather comprehensive category embracing many forms of individual underwater activity, such as skin diving, submarine escape, underwater demolition team activities, underwater swimming, mine detection and demolition, beach reconnaissance, individual aspects of miniature submersible craft operation, and so forth. Shallow-water diving may be defined as that type of individual underwater operation that usually does not exceed 100 feet in depth and is performed in water relatively adjacent to land, such as streams, rivers, bays, inlets, harbors, and so forth, and employs self-contained apparatus of some variety, of which there are many.

In the category of shallow-water diving the activities of underwater swimmers, whatever their function, have now become a greatly expanded field of offensive operations with considerable wartime potential against targets afloat and ashore. This phase of human underwater activity is to be the major topic of dis-

cussion during this symposium.

As a result of the exploitations of human underwater swimmers in groups, there has developed an extensive nomenclature; as examples the following names which are all somewhat synonymous are encountered in the historical accounts: underwater demolition teams, limpeteers, mine clearance and demolition teams, charioteers, frogmen, beach reconnaissance teams, underwater raiders, submarine assault teams, boom clearance parties, human torpedoes, X-craft crews, and more recently, underwater swimmers.

The history of World War II reveals that the U. S. Navy made a relatively small and isolated effort toward development and attainment of any substantial stature in the underwater swimmers' form of warfare. This seemed to be at least partially the result of opinion that the missions of underwater demolition teams were somewhat suicidal in nature and therefore were not endorsed or condoned in the U. S. warfare philosophy. European nations, on the contrary, devised and developed attacks by underwater swimmers to a considerable degree of perfection and attained a rather surprising amount of success. It is estimated that approximately 150,000 tons of allied shipping were destroyed by limpeteers and underwater demolition teams. Several Mediterranean harbors were the scene of the most signal success by swimmers. In fact, this method of attack rendered these harbors almost untenable by allied shipping and was a source of distress and alarm to the British as well as the Americans, calling for novel and unusual retaliative measures. The persistence of the underwater swimmers' attacks dictated that whenever a ship came to anchor in the allied Mediterranean ports, a watch system be imposed wherein divers traversed the keels of anchored ships on an hourly schedule to remove and dispose of the limpets or other explosive ordnance charges installed by the underwater swimmers. These wartime activities of the underwater demolition teams have engendered a few narratives, some of which were verified, others were not. Of the unverified variety the speculated veracity status renders them no less amusing. One such incident relates that a diver while making the routine Mediterranean anchorage night patrol of a ship's bottom encountered an enemy limpeteer attaching his charges. The ensuing struggle was perhaps the prime incidence of individual wartime combat underwater and thereby established a precedent for warfare in a new environment. The diver in this incident dispatched his adversary by ingeniously employing his only weapon, the diving knife, and placed this episode in the verified variety by producing the corpus delicti upon his ascent.

Europeans were not only operationally successful in this form of warfare, but were especially proficient in design and development of apparatus. However, emotional inaptitude resulted in failure of at least two UDT missions as is exemplified by the following incidents. A swimmer having successfully reached his target and attached his charge was, while reflecting on the sad fate of the personnel of his target, emotionally overwhelmed to the extent that he surfaced and boarded the ship, gave the alarm by ringing the ship's bell in time to prevent the explosion, and was happily interned as a prisoner of war. On another occasion, a swimmer had reached his target, but attaching his limpets required working near barnacle-covered piling which eventually lacerated his suit. Fearing doom by cold or drowning, he surfaced and surrendered without damage to the target ship.

I invite your attention to the fact that thus far this presentation has displayed little in support of the originally announced title to elicit the major problems of underwater swimmers. Please bear with me while I attempt to create a setting of the announced preliminary goal by making a few statements that at first blush might not appear pertinent.

It requires no great intellect to discern that the Armed Forces in all their peacetime activities point their research and development training and planning toward attaining a proficiency and readiness for war. John Paul Jones is credited with an utterance that seems as apropos as it is ungrammatical with its split infinitive, "In times of peace it is necessary to prepare and to always be prepared for war".

In view of this preamble let us now examine the major problems of underwater swimmers as influenced by war-readiness consideration.

I would propose that the prime problem of underwater swimmers today is countermeasures initiated and imposed by the enemy. It may surprise many among you that anyone would contend that enemy action composes the major problem of underwater swimmers. Since I have embarked on the issue of enemy action as a threat to underwater swimmers, it seems pertinent to mention that the element of detection, such as sonic signature, bubbles produced by apparatus leaks, and the need for silence and concealment, usually necessitating night operations, all pose underwater swimmer problems. Obviously, this problem is more physical than physiological. It is perhaps erroneous to place it at the top of the list and it is only so placed in this dissertation to emphasize its importance or to prevent minimization of its import. Anyone who has witnessed the extraordinary effectiveness of detonated submerged charges on the human body underwater needs no edification from this source to the effect that countermeasures currently are in need of improvement. To date our armamentarium contains little or nothing to provide a measure of protection in this particular vulnerability of the underwater swimmer. Personally, the only method of protection I have ever heard mentioned is for the swimmer, in the presence of underwater attack, to extrude as much of his body as possible from the water. Such surfacing is tantamount to failure of the mission and surrender. It is hoped that studies currently in progress at the Mine Countermeasures Station, Panama City, Florida, will furnish basic information concerning underwater blast that will point the way to providing some swimmer blast protection.

Oxygen toxicity demands a prominent position on the list of underwater swimmers' problems. Consideration of this entity, however, reveals that its implications are so intimately associated with the consideration of compressed air illness, it is probably prudent to discuss the two conditions simultaneously. These rather entrancing interrelationships are well exemplified by a narrative of British experiences during the late war. German mine-laying activities had drastically restricted shipping within the coastal waters surrounding the British isles to an extent that threatened survival of water traffic and overwhelmed the capabilities of conventional deep-sea diving to cope with these enemy activities. Utilization of shallow-water divers, with air as the breathing medium (from multiple small tender craft) dictated the need for portable compressors, air banks, hose, and other apparatus, much on a par with deep-sea diving. Further, since the area to

be searched for mines was considerable and the time factor critical, it was necessary to surface and submerge the divers frequently as the area amenable to search on a single sortie was of diminutive radius. This type of diving operation with frequent traversing of the depth in each direction was soon doomed by an unacceptable incidence of decompression sickness, even after the single-sortie radius was enlarged by resort to self-contained apparatus. Failure of the missions due to bends led to the adoption of oxygen as a breathing medium, despite the meager knowledge existent at that time regarding such utilization. Initial success and optimism soon faded when the specter of oxygen poisoning disabled the diver as a result of nausea or muscle spasms, or else this led to complete inactivation or loss of the diver with or without subsequent recovery of the bodies as a result of convulsions. Thus, on the one hand, we are confronted with the dilemma of bubble formation and its sequelae and the dramatic oxygen seizures on the other. Many students of the physiological aspects of diving contend that somewhere in the realm of gas mixtures as breathing media there is a happy and useful mean with a minimum of oxygen toxicity and bends incidence. Some success has been attained in this direction. However, full realization has not been attained and requires further exploration. Considerable investigative effort in this field is currently in progress. It is purposeless to dwell on the disabling, if not lethal, results of compressed-air illness before such a group as this. Oxygen convulsive seizures are dramatic, alarming, as well as disabling, but appear to have no eventual detrimental effects except to create in the victim a fear of future attacks.

Since there is factual evidence that cold affects compressed-air illness incidence, and I personally am convinced that cold through internal shunting of the blood stream affects oxygen tolerance under pressure, we must include temperature in the items that plague the underwater swimmer. This implication of the temperature effect on oxygen toxicity is aside and apart from the limitation of endurance by virtue of cold tolerance on human activities.

I fully realize that so far I have spoken of only a few of the main underwater swimmer problems, and time will not permit any further extensive treatment. However, in the interest of completeness, I shall portray very briefly the problem areas in regard to individual underwater activities, with a career cycle to highlight the problems.

The personnel selective procedure whereby a candidate acquires underwater swimmer status demands foremost the absence of physical defects or potential defects and the candidate must pre-eminently possess a stable psyche and phlegmatic personality. The possession of a temperament free of alarmist characteristics is essential. Ideally perhaps a personality bordering on a vegetative status might be the superlative.

In some quarters there is thought that a background of a thoroughly trained and experienced deep-sea and shallow-water diver is a prerequisite. At least the basic training period attempts to attain this status. A thorough knowledge and familiarity with all types of diving apparatus is sought. Those who have gadgeteer tendencies in this respect seem to possess the innate apparatus curiosity that connotes subsequent success. Once these preliminary hurdles are cleared, the swimmer obtains operational status by team and beach group assignment for his postgraduate training.

The intricacies of operational training now inform the swimmer that his missions will require transportation to the vicinity of the operational area by submarine or other secretive craft, transportation to the immediate target area by his own swimming efforts or by individual craft with restricted power and speed, or will require the swimmer himself to provide the propulsive power. He learns that in these operations he will be wet, he will be cold, he may contract the bends or an oxygen seizure, he must work in the dark, he must learn to get through nets or other barricades, he must avoid detection by sentries, searchlights, and electronic detectors, his apparatus must not leak or fail, he must not lose his course in unfamiliar territory, and above all he must complete his mission successfully, and he must not dwell on the fact that he may not return. In view of all these problems it is my opinion that this military vocation requires a stout physique, a stout intellect, and a stout heart.

2.1 INTRODUCTION TO SEMINAR ON OXYGEN TOXICITY

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Between 1870, when Paul Bert began his studies of increased ambient pressure effects on animals, and the early 1930's, oxygen toxicity was essentially a matter of academic interest. The reason for this is evident in that there is no naturally occurring situation wherein oxygen tensions approaching toxic levels exist. Prior to World War II the use of pure oxygen at increased ambient pressure to speed decompression after helium-oxygen, deep-sea diving and during World War II, in the military employment of self-contained diving apparatus using oxygen as a breathing medium, the toxicity of oxygen became a practical naval problem. At present it is one of the most important limiting factors in free diving.

Some of the most intensive studies aimed at elucidating the underlying biochemical mechanisms of oxygen toxicity upon the central nervous system were carried out at the University of Pennsylvania by Dr. William Stadie and Dr. Neils Haugaard. Dr. Haugaard will begin the Seminar on Oxygen Toxicity by reviewing the more important studies of effects of high oxygen tensions upon brain enzymes, to be followed by Dr. J. W. Bean, who will discuss hormonal aspects of oxygen toxicity, and Dr. S. Stein, who will speak on neurophysiological effects of oxygen at high partial pressures. I shall discuss the respiratory and circulatory actions of high oxygen pressures.

2.2 EFFECT OF HIGH OXYGEN TENSIONS UPON ENZYMES

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INTRODUCTION

That the toxicity of oxygen at high pressure is related to inhibition of enzyme reactions was already envisaged by Paul Bert.[1] We find the following statement in his fascinating book, "Barometric Pressure", in which the phenomenon of oxygen poisoning in animals is so vividly described:

> "In summary, consumption of oxygen, breaking down of glucose in the blood, all chemical phenomena which can be measured easily, appear to be considerably slowed down by the action of oxygen under high tension."

This was in 1878 at a time when the "chemical phenomena" in tissues were little understood in terms of enzyme chemistry.

Until the second World War little attention was paid to the subject of oxygen poisoning. At that time, spurred by the practical importance of the problem, Dickens in England and Stadie and his co-workers in this country initiated systematic studies on the inactivation of enzymes by oxygen.

Very similar results were obtained by the two groups. When the respiration of tissue slices was studied at high pressures of oxygen or after exposure to oxygen at elevated pressure, [2, 3, 4] it was found that oxygen uptake and carbon dioxide production were diminished, indicating a depressant effect of oxygen on tissue enzymes.

Brain tissue appeared to be more susceptible to the action of oxygen than other tissues. [2, 3, 4] However, the time necessary for oxygen to exert an effect on respiration in vitro, even with brain tissue, was much longer than the time required for oxygen at comparable pressure to cause violent symptoms and death in the animal. In addition it was found that the respiration of tissue slices obtained from an animal killed by exposure to high pressures of oxygen was not significantly different from normal. In agreement with these observations was the finding that the total oxygen consumption of the intact mouse at 8 atmospheres of oxygen was not seriously depressed at the acute stage of oxygen poisoning.[5]

These observations tend to rule out a general depression of oxidative metabolism as the direct cause of oxygen poisoning in the animal.

MECHANISM OF INHIBITION

Many enzymes have been found to be inactivated in vitro.[6, 7, 8] One class of enzymes, those depending on the presence of free sulfhydryl groups in the molecule, was found to be inactivated with particular ease. Succinic dehydro-

genase is an example of such an enzyme. That this enzyme was inhibited by oxygen at high pressure was already established by Libbrecht and Massart. [9] The mechanism of inhibition as we picture it is illustrated in Figure 2.2-1.

The enzyme is thought to exist in two states, an active one, in which the sulfhydryl groups are free, and an inactive state, in which the SH groups are oxidized to form S-S bridges.

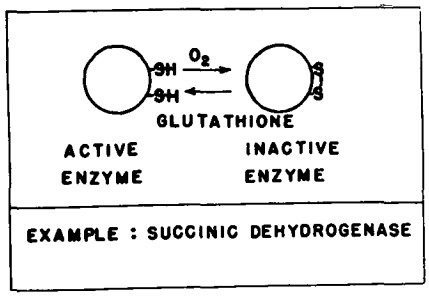

Figure 2.2-1 Inactivation of SH-enzymes by Oxygen

The inactive enzyme may be formed by oxidation of SH groups much in the same way as two molecules of reduced glutathione may be oxidized to form a molecule of oxidized glutathione. This mechanism of action is supported by the observation that the oxygen-inactivated enzyme may be reactivated by reduced glutathione and by the fact that succinate or malonate protect against the inhibitory action of oxygen. [6, 7] These substances, one the substrate of the enzyme, the other a competitive inhibitor, are believed to become attached to the enzyme in such a way that they shield the sulfhydryl groups, thus preventing their oxidation by oxygen.

ENZYME INACTIVATION AND OXYGEN TOXICITY

As in the studies of the effect of oxygen at high pressure on respiration of tissue slices, a constant finding was the disappointing one that more drastic conditions were necessary to inactivate enzymes than were required to produce the symptoms of oxygen poisoning in the animal. It was also noticed that many enzyme reactions that were easily inhibited when extracts or homogenates were used were little influenced by oxygen when studied in tissue slices.

I think that it may be said that the enzyme studies have given strong support to the view that inactivation of enzymes plays an important role in oxygen poisoning, but that they have failed to provide us with an understanding of the phenomenon in terms of inhibition of one or more specific enzymes.

There are some enzyme systems whose inactivation by oxygen may prove to be of special significance in relation to the problem of oxygen toxicity. Jowett and Quastel[10] in 1933 showed that the glyoxalase activity of human red cells and rat tissues was progressively inhibited in the presence of 1 atmosphere of oxygen. They attributed this inactivation to the oxidation of reduced glutathione which is a coenzyme in this reaction. Glyoxalase, an enzyme catalyzing the transformation of methylglyoxal to lactic acid, has always been a stepchild whose role in cell metabolism has been difficult to understand. Important for this discussion is, however, the fact that its coenzyme, reduced glutathione, contains a free sulfhydryl group.

We know now, but not when the studies were done, that three other enzyme

reactions inhibited by oxygen depend for activity on coenzymes containing SH groups. These reactions are illustrated in Table 2.2-1.

Reaction	O_2 Effect	Coenzyme
Oxidation of Glyceraldehyde-3-P	+	Glutathione
Oxidation of Pyruvate	+	Lipoic Acid
Acetylation of Choline	+	Coenzyme A

Table 2.2-1 Inhibition by Oxygen of Enzyme Reactions Involving SH-coenzymes

Glyceraldehyde-3-phosphate dehydrogenase was found by Dickens to be inactivated by oxygen.[7] It is now known to contain the coenzyme, reduced glutathione. The oxidation of pyruvate by brain was found by Dickens to be particularly susceptible to the inhibitory action of oxygen.[4] The details of this reaction are still not completely understood, but we do know that alpha-lipoic acid is a coenzyme in one of the steps of the reaction. This substance in its reduced form contains two sulfhydryl groups. Cocarboxylase is another coenzyme involved in pyruvate oxidation. It is now thought that this substance may possibly exist in a reduced form containing a free-sulfhydryl group. Finally, Stadie and his co-workers[11] found that the acetylation of choline by brain homogenates, although not by brain slices, was rapidly inactivated by oxygen. This enzyme reaction has now been shown to be dependent for activity on the presence of coenzyme A, another coenzyme whose mechanism of action involves the participation of an SH group.

The findings that these enzyme reactions, dependent on the presence of SH-coenzymes, are inhibited by oxygen suggest the possibility that in the intact animal the acute symptoms of oxygen toxicity may be related to an oxidation of essential coenzymes rather than to an inactivation of the tissue enzymes themselves.

In the experiments of Lambertsen and co-workers on oxygen poisoning in intact animals, a striking feature of the chain of events was a latent period of considerable duration preceding the rapid development of the characteristic symptoms. Furthermore, when the exposure of the animal to oxygen at high pressure was interrupted by an intermittent short period of exposure to a lower tension of oxygen, the time for development of symptoms was increased. These observations are in agreement with a mechanism of oxygen toxicity involving a slow exhaustion of an essential metabolite, such as a coenzyme, that is easily regenerated by the tissue on return to a normal tension of oxygen.

EXPERIMENTS WITH BRAIN HOMOGENATES

I should like to conclude by presenting some experiments which may possibly have some bearing on our subject. Rat brain homogenate was equilibrated at 37°C. in Warburg vessels containing a bicarbonate buffer. The vessels were gassed with 5% CO_2, 95% N_2, or with 5% CO_2, 95% O_2. After different periods of time ferricyanide was tipped in from the side compartment and the carbon dioxide evolved determined manometrically. Ferricyanide is a mild oxidizing agent and at 37°C. reacts with easily oxidizable substances such as compounds containing free-SH groups. Ascorbic acid is another compound present in tissue which reacts with ferricyanide under the conditions of this experiment. For each molecule of ferricyanide reduced, a hydrogen ion is produced. The extent of oxidation may, therefore, be measured by the evolution of carbon dioxide from a bicarbonate buffer. Ferricyanide reacts only at higher temperatures with reducing substances such as glucose. The reduction of ferricyanide by tissue extracts is probably caused to a major extent by the presence of reduced glutathione. The results of the experiments are illustrated in Figure 2.2-2.

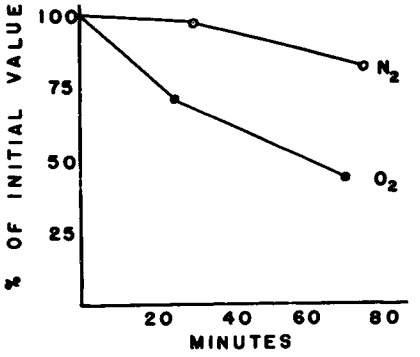

Figure 2.2-2 Oxidation of Ferricyanide by Rat Brain Homogenate

In the presence of nitrogen there is only a slow disappearance of the easily oxidizable substances in the brain homogenate. When oxygen is present, however, there is a much more rapid disappearance of these substances.

I am only presenting this observation here because it provides some experimental support to the hypothesis that at high tensions of oxygen, easily oxidizable essential metabolites such as the SH-containing coenzymes may become oxidized and thereby prevented from assuming their normal function.

In this connection it is of interest that Pfeiffer and Gersh[12] found that cysteine, an SH-containing amino acid, had some effect in prolonging the preconvulsion time in cats exposed to 7 atmospheres of oxygen.

At present we have only inconclusive evidence that the mechanism of oxygen toxicity involves oxidation of SH-coenzymes, but the concept may prove to be a fruitful working hypothesis in further studies on oxygen poisoning. Such studies might involve the determination of the concentration of free-sulfhydryl groups in tissue preparations exposed to oxygen or in tissues from animals killed by high pressure of oxygen. If possible, the levels of the individual SH-coenzymes in tissues should be determined under different conditions of exposure to oxygen.

SUMMARY

In summarizing we may say that the studies on oxygen poisoning from an enzyme point of view have provided support for the concept that inactivation of tissue enzymes plays an important role in oxygen toxicity.

A general depression of enzyme activity is not involved. Many enzymes are completely unaffected by high tensions of oxygen.

Although we have not so far been able to ascribe the acute symptoms of oxygen poisoning to an effect of oxygen on a specific enzyme, the evidence points to an involvement of a few particularly sensitive enzyme reactions. It does appear that in brain tissue the oxidation of pyruvate is more easily inhibited than the oxidation of other substrates.

It is proposed as a working hypothesis that the toxic action of oxygen at high tension may be related to an oxidation of essential metabolites such as coenzymes containing sulfhydryl groups rather than to inactivation of enzymes directly.

2.3 HORMONAL ASPECTS OF OXYGEN TOXICITY

John W. Bean
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INTRODUCTION

The toxic effects of oxygen evoke such a wide variety of reactions and excite so many physiological systems that it is only to be expected that hormone mechanisms in general might be significantly involved, and particularly those of the hypophyseal-adrenal system, since oxygen toxicity constitutes a stress of considerable severity.

In this general background and the early enthusiasm regarding the use of ACTH and adreno-cortical factors in the treatment of rheumatoid arthritis, it occurred to us that possibly the more-or-less permanent neuromuscular disabilities which can be induced in animals by repeated exposure to oxygen at high pressure (OHP)[13, 14] might be relieved by similar treatment, although Roentgen ray examination by Dr. Holt failed to show typical arthritic changes. ACTH and cortisone were therefore administered, but in these preliminary experiments it was quite evident that instead of improvement, the general condition of the animals deteriorated.

THE ADRENAL GLANDS

At that time no information regarding the reaction of the adrenals to OHP was available, so experiments were undertaken to determine if possible just what the reaction might be. Now it is one thing to place an animal in OHP and then examine the adrenal for changes typical of those induced by stress, but quite another to show that the adrenal changes, whatever they might be, are due to the OHP per se and not simply to the secondary stress conditions, such as the oxygen convulsions and respiratory difficulty which OHP induces. However, careful analyses carried out in 1950 and 1951 showed that aside from the secondary stress effects OHP per se does evoke adreno-cortical reactions typical of those seen in non-specific stress, Figure 2.3-1,[15] and certain features of these experiments led to the conclusion that these "adrenal changes were casually related to the manifestation of the adverse effects of OHP".[15]

EFFECT OF HYPOPHYSECTOMY

In a continuation of this study of adreno-cortical involvement, hypophysectomy was chosen as a method of eliminating adreno-cortical influence without introducing the complication, inherent in adrenalectomy, of removing medullary hormones, whose influence in defense reactions has been recognized since the early work of Cannon. On generally accepted principles[16] it was argued that if the adreno-cortical reaction in OHP found in our previous experiments "constitutes a part of a general protective response of the organism to stress and that this adrenal response is dependent upon the integrity of the pituitary, hypophysectomy might be expected to intensify the adverse reaction to OHP. But in our experiments it diminished rather than intensified the reaction to OHP", from which it would follow that

Figure 2.3-1
Effect of Oxygen at High Pressure on Adrenal Glands

A

Gland of non-exposed rat. The zona fasciculata of the cortex contains large amounts of lipid (black)

B

Gland from rat exposed to OHP. The adrenal cortex is hypertrophied, the glandular cells of the zona fasciculata and zona reticularis are enlarged and lipid is depleted from these portions of the cortex.

"the protection which hypophysectomy affords against OHP is attributable to the elimination of that adrenal response which in other forms of stress constitutes a part of a defense or adaptive mechanism"[17, 18] Figure 2.3-2. Supporting this interpretation was the finding also that "ACTH counteracts, to some extent at least, the protective action of hypophysectomy against the adverse effects of OHP. For example, in one series of experiments the number of reactions to OHP in the hypophysectomized rats injected with ACTH was twice as great as that for non-injected hypophysectomized animals and in fact was equal to the number in the non-operated control animals".[18] From still other experiments[19] it was concluded that "hypophysectomy protects against pulmonary damage inflicted by oxygen by eliminating or diminishing those principles which, released in the normal animal, augment the susceptibility of pulmonary tissue, particularly the vascular bed, to the injurious effects of oxygen in high concentrations. Corticotropin and cortical hormones, among them cortisone, constitute important parts of this augmentatory mechanism but are not essential to the precipitation of injury by oxygen".[20] These conclusions found later support in the work of others in this country[21] and abroad,[22] as well as in work of our own which showed that adrenalectomy itself provides a measure of protection against the adverse effects of OHP.[23] Figure 2.3-3 A and B. As was pointed out above, the evidence from adrenalec-

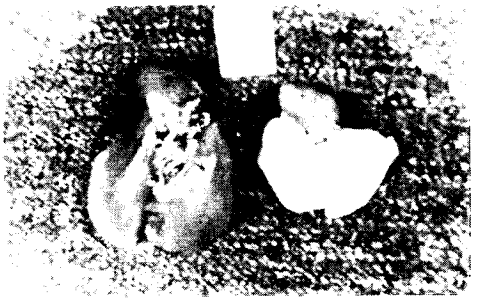

Figure 2.3-2 Protective Action of Hypophysectomy against Pulmonary Damage by Oxygen at High Pressure

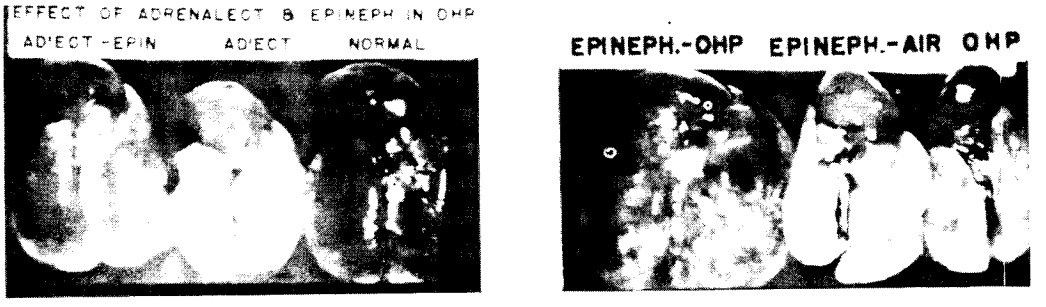

Figure 2.3-3 A and B Protective Action of Adrenalectomy against Pulmonary Damage by Oxygen at High Pressure and the Partial Nullification of this Protection by Epinephrine

tomy alone is complicated by the fact that such a procedure also eliminates medullary factors, and there is reason to suspect[24] that adrenalin might enhance the toxic influence of OHP. Our later experimental investigation of this question showed that adrenalin does indeed increase the adverse effects of oxygen in general but especially those of pulmonary damage and of permanent motor disabilities in both the adrenalectomized (Figure 2.3-3A) and the non-operated animals (Figure 2.3-3B).[25]

THE SYMPATHETIC NERVOUS SYSTEM

This finding that a sympathomimetic substance markedly augments oxygen toxicity, together with other indications of sympathetic nerve discharge in certain phases of the more severe oxygen reactions, suggests that the sympathetic nervous system might be a significant contributor to the adverse effects of OHP. Experiments were therefore carried out in which attempts were made to eliminate sympathetic effects by sympathetic blocking agents, particularly those of SKF501 (9-fluorenyl-N-ethyl beta chlorethylamine) and T. E. A. (tetraethyl ammonium chloride).

It was found as reported by Mr. Johnson at the Fall Meetings of the Physiological Society in 1954 that these agents provide an appreciable degree of protection against certain phases of oxygen toxicity, Figures 2.3-4 and 2.3-5, and while the effects of dibenamine were less definite than those of SKF501 and T. E. A., the data justify the conclusion that the sympathetic nervous discharge contributes appreciably to the enhancement of the toxic reaction in OHP, especially that of the lungs. These data[26] supply some experimental substantiation for the view that the pulmonary edema and hemorrhage induced by OHP in the intact animal are, to some degree at least, of neurogenic origin via the hypothalamus and sympathetico-adrenal system, including an increased secretion of adrenalin and nerve discharge to thoracic viscera and the lungs themselves.

EFFECTS OF CARBON DIOXIDE

Although the exact method of its action has not been fully established, it is generally agreed that a relatively small increase in carbon dioxide, whether of exogeneous or endogenous origin, is peculiarly effective in augmenting most of the toxic reactions in OHP, especially those of the neuromuscular and central nervous systems,[27-36] but evidence as to what influence carbon dioxide might have on the pulmonary reaction has been all but lacking. Experiments carried out to determine this showed clearly that carbon dioxide -- at least in OHP -- augments this pulmonary damage. Various explanations might be offered for this; for example, Ohlson presents data[37] and holds that increased carbon dioxide acting on the blood side of the capillary wall is the cause of the pulmonary damage in oxygen. But the fact that carbon dioxide markedly augments the central nervous system effects of OHP suggests the possibility that its augmentative action on the pulmonary damage might have a neurogenic component.

The hypothalamus is sensitive to stressing agents as insulin, adrenalin, hypoxia,[38] and carbon dioxide, and from its close anatomical and functional relationship to the hypophyseal-adrenal[39, 40] and the sympathetico-adrenal systems,[40, 41] one may infer that it is peculiarly involved in the various reactions to OHP

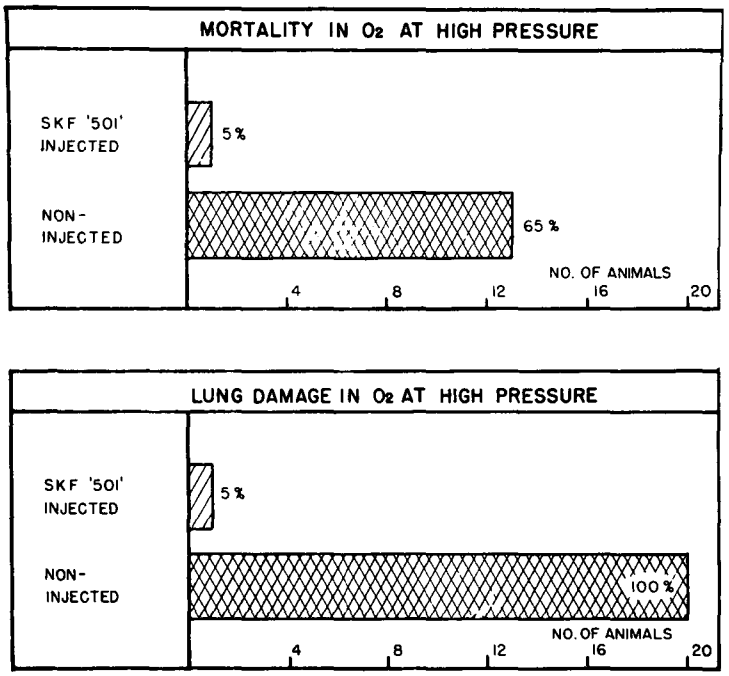

Figure 2.3-4 Typical Protective Action of SKF501 against Mortality and Lung Damage by Oxygen at High Pressure

Figure 2.3-5 Protective Action of T. E. A. against Lung Damage by Oxygen at High Pressure

through central action of carbon dioxide. It is significant therefore that sympathetic blocking agents SKF501 and T. E. A. were found to afford an appreciable degree of protection not only against the lung damage induced by OHP itself, but also against the augmentation of this damage by OHP and carbon dioxide in combination.[42] Such results indicate that the augmentation by carbon dioxide is in large part of central origin, possibly within the hypothalamus where carbon dioxide in certain concentrations is thought to have a pronounced excitatory action,[43] and that it is mediated via the sympathetic nervous discharge to the lungs and possibly also the adrenal medulla.

A great volume of experimental data has accumulated over the years which convincingly shows that alterations in metabolism markedly affect the susceptibility to, and the severity of, the adverse action of OHP.[31, 36, 47] In general, anything which tends to elevate the metabolism should augment the reaction to OHP because of, among other changes, the increased production of carbon dioxide which assumes greater importance where OHP, preventing the normal reduction of the hemoglobin, interferes with the dual function of the hemoglobin in carbon dioxide transport,[27, 29, 44] although the significance of this mechanism has been questioned by some authors.[45, 46]

Certain endocrine factors significantly increase metabolism, and at least a part of their augmentative action on the adverse effects of oxygen has been explained on this basis; for example, adrenalin is said to increase oxygen toxicity by an elevation of metabolism[24] and the effects of thyroid are similarly explained.[24, 34] Our own recent experiments with Mr. Smith and Mr. Bauer show that thyroid extract, or thyroxin,[48] also profoundly augments the pulmonary damage induced by oxygen. See Figure 2.3-6. A considerable part of the protection which hypophysectomy affords against the adverse effects of oxygen, especially those of the lung, would appear therefore to be attributable to the consequent removal of thyrotropic hormones.

Figure 2.3-6 Effects of Thyroid on Lung Damage by Oxygen

It is important, however, to note that thyroid may influence oxygen toxicity by means other than that of metabolic change. Our experimental evidence[18] has shown that thyroid administration enhances susceptibility to OHP before there is any evident elevation of metabolism.

Alterations in metabolism induced by hormonal factors may influence the toxic reaction to oxygen by changes in carbon dioxide -- possibly through central stimulation of the sympathetico-adrenal system and a release of adrenalin, or of the hypophyseal-adrenal system and release of ACTH and adreno-cortical factors which enhance the adverse effects of oxygen.[20] But there are other possibilities. For example, the increased metabolism of tissues induced by adrenalin may entail an increased 'utilization' of cortical hormones and a consequent release of more ACTH and cortical factors;[49] or adrenalin itself acting as a stress agent on the

hypothalamus[38] and through the hypophyseal-adrenal system[39] may release increased quantities of adreno-cortical factors. Furthermore, the possibility of some more direct influence of hormones such as thyroid and adrenalin on the vascular bed cannot be entirely dismissed.

CAPILLARY PERMEABILITY

One of the outstanding features of pulmonary effects of oxygen and their augmentation by various hormone factors is the well-defined influence on pulmonary blood vessels, in which there occurs an increased permeability, with hemorrhage, congestion, edema, and loss of proteins.[31, 36, 20] But these vascular effects of OHP and possibly of oxygen at atmospheric pressure are not confined to the pulmonary tissues for, as was reported years ago,[50] such effects are to be found also in the brain and have been offered in explanation of some of the central nervous system's reactions to OHP, especially the permanent motor disabilities[13, 14] and the deterioration in the higher functions of the central nervous system.[51, 52] Our repeated exposure of young rats and baby chicks to OHP[55] not only induced permanent motor disabilities, decreased growth, and altered higher functions of the central nervous system, but also adversely affected visual function.[55] It is more than coincidental therefore that the vasculature of the retina, in reality an extension of cerebral structures, is so markedly affected in oxygen[53] and in retrolental fibroplasia and that in many cases of the latter there is an associated subnormality in the higher functions of the central nervous system and frequently even imbecility.[54]

SUMMARY

While the vascular bed is an important site of action of OHP and the augmentatory influence of hormone factors, it is by no means the only one, for under proper conditions almost every tissue of the body can be shown to be adversely affected by OHP.[31] Nor would it seem justified to ascribe the various manifestations of oxygen toxicity to some single or key factor.

The presence of carbon dioxide even in relatively small amounts is particularly effective in precipitating and augmenting the toxic manifestations of oxygen in the intact animal. But obviously there is a more intimate effect of oxygen than that of an alteration in carbon dioxide. It was suggested[56] that a poisoning of enzyme systems might account for some of the oxygen reactions and an apparent increase of tissue acidity observed in some of our early experiments. The accumulation in acid metabolites found in isolated tissues exposed to OHP by Cass[57] is of interest in this connection and is reminiscent of the paradoxical state of "Hyperoxic Anoxia",[60] which may operate as a stress through the hypothalamus and the adrenal cortex. Our own experiments on isolated tissues[58, 60] and on enzyme systems[59] indicate clearly the importance of enzyme poisoning by OHP, as do those of many others,[9, 36] particularly those of Stadie and Haugaard,[6] Haugaard,[8] and Dickens,[61] which emphasize the probable importance of the adverse influence of oxygen on SH enzymes.

2.4 NEUROPHYSIOLOGICAL EFFECTS OF OXYGEN AT HIGH PARTIAL PRESSURE

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INTRODUCTION

It is with some trepidation that I shall attempt to discuss briefly with you the existing data concerning the neurophysiological aspects of our problem. I say trepidation because, as a neurophysiologist, I am acutely aware of the scarcity of truly "neurophysiological" work being carried on on the magnificent quandry presented to us by oxygen toxicity of the central nervous system; and one of the points I should like to stress during this presentation is this lack of information contrasted with the numerous avenues of investigation open to us. To say that no knowledge exists as to the neurophysiological factors in hyperoxic toxicity would be cursory and would neglect several valuable studies by very competent workers, about which I shall say more later.

The problem of neural mechanisms in hyperoxic convulsions, as I see it, is actually no different than the one presented to Hypocrates by the "sacred disease" 2000 years ago, or that involved in the production of grand mal type fits by electroshock, Metrazol, organic brain disease, or other diverse agents; for we can say with authority now that the seizures of oxygen toxicity are in no wise different neurophysiologically from grand mal epilepsy.

HYPEROXIC CONVULSIONS

We know from many studies that the neural insult -- be it a direct toxic action of oxygen in the form of free radicals or peroxides on the cellular enzyme systems, be it the action of accumulated carbon dioxide at the cellular level due to a breakdown of the carbon dioxide-hemoglobin transport system, be it the result of endocrine dysfunction, or be it a combination of all factors -- we know that the neural insult is sired by the respiratory system and delivered by the blood stream. Once the central nervous system is activated, a cerebral dysrythmia ensues, which if allowed to go on develops into a generalized convulsion. The convulsion is like an ordinary epileptic one, and two or three minutes of kicking are followed by about ten minutes of unconsciousness, with gradual recovery through a confused state if the exciting factor is removed in time. Otherwise the process continues until death takes matters from the physician and gives them to the mortician. However, if the exciting factor is removed in time, the process is reversible and apparently without any well-documented, permanent damage to the central nervous system. In a letter from J. B. S. Haldane, received prior to his becoming persona non grata to our State Department, wherein he tells of his wife's experiences with hyperoxia, he states, "So far as I know, the person who has had the most oxygen convulsions is my wife. She has had five. Her intellect appears to be unaffected. She is rather emotional, but I do not know that this is an effect of the convulsions."

The neurophysiologist properly wants to know not so much the exact nature of the insult (for the central nervous system seems to use the same reaction pattern -- a seizure -- for many dissimilar insults) but once given the neural excitant, he wants to know: 1) Where do the fits start in the brain? 2) When do they start? 3) By what routes do they spread? 4) To what areas of the central nervous system do they spread? 5) How can the seizures be modified or suppressed? And finally, 6) what is there about the exciting cause that can wreak such havoc with the neurons of the brain? Does it act on one small area or group of cells to depress or excite them, or does it act on many cells at once? Does it provoke a fit by activating a release phenomenon, or is it a general and powerful excitant in its own right? These questions it can be readily seen, if answered, would illumine not only the symptom complex of hyperoxic convulsions, but all maladies which have as a primary manifestation this central nervous system reaction.

ELECTROENCEPHALOGRAPHY

Because what is known neurophysiologically about oxygen toxicity is limited, I believe there is time to mention hastily almost all of the existing neurophysiological findings. Lennox and Behnke (1936), Gersh and Cohn (1944), Stein and Sonnenschein (1950, 1953), and Batini, et al (1953) have all collected data establishing the fact that at least electroencephalographically the seizures caused by high partial pressures of oxygen are indistinguishable from grand mal epilepsy. In cats the fits are periodic, last from a few seconds to a few minutes, and are followed each time by a quiet period in which the EEG potentials are almost isoelectric. Twenty to forty of these intermittent seizures may occur in a period of one-half to one hour at a sustained pressure of 75 p. s. i. (gage), that is, at 5 atmospheres. After an hour, however, this activity of the brain diminishes and ultimately disappears, leaving nothing but a flat-line trace. The seizure pattern at high-oxygen partial pressure consists of high-amplitude, fast spikes which break off rather sharply to low-amplitude, fast activity or to a relatively isoelectric state. Considerable variation exists in the animals under test -- as it does in man -- as to onset and duration of individual fits, but the tracings are strikingly uniform.

It is of interest in passing to note that the seizure patterns appear during, or just after, the sharp and extreme rise in "cerebral oxygen tension", as reported by Gersh, Davies, and Larrabee (1945) and confirmed by Stein, Sonnenschein, and Perot (1953).

CARBON DIOXIDE SEIZURES

Carbon dioxide has been intimately related to the etiology of hyperoxic convulsions, but it seems unlikely that its action alone incites the seizure. The convulsive activity of carbon dioxide on the central nervous system is manifestly different from that caused by oxygen, both in the EEG pattern and in the clinical picture. The brain wave record of a subject inhaling high concentration of carbon dioxide is marked by very fast, low-voltage spikes, and clinically one sees opisthotonos and a preponderance of tonic activity. The carbon-dioxide seizure has been termed a "decerebrate fit" to distinguish it from hyperoxic convulsions and was documented by Gyarfas, Pollack, and Stein (1949).

In the past during conversations with naval medical officers, diving personnel, and people engaged in underwater swimming operations, I have noted occasionally a lack of appreciation of the distinction between these two entities, since it was often the case that an incident described as a hyperoxic convulsion was obviously on closer examination an example of a true "decerebrate fit" caused by breathing an excess of carbon dioxide. It must be remembered that a man even though swimming with oxygen equipment, may still build up a toxic level of carbon dioxide within the closed system. I feel that the marked difference between hyperoxic seizures and decerebrate fits should be emphasized more strongly in the instructional program of those concerned with the underwater swimmer.

THE CENTRAL NERVOUS SYSTEM

In 1938 Bean conducted a study attempting to determine the importance of some of the central nervous system structures which might be peculiarly involved as the site of action of the neural insult in the induction of these convulsive attacks. Using decorticate and decerebrate dogs exposed to oxygen at 5 to 6 atmospheres pressure, he found that neither the cortex nor basal ganglia were essential to the induction of oxygen poisoning reactions, which he concluded must arise from sites below the superior colliculi.

Juxtaposed to these findings we have the experiments of Gersh dealing with the site of origin of the seizures. In 1944 he made the following observation in cats.

(1) Complete sympathectomy did not prevent hyperoxic convulsions.

(2) Removal of one or both motor cortices did not prevent hyperoxic seizures.

(3) Removal of both motor and premotor cortices bilaterally was also of no avail.

(4) Hemidecortication did not prevent them.

(5) Spinal cord section in the cervical and thoracic region did not prevent the motor phenomena below the lesion.

(6) Decorticated and decerebrated cats did not show any convulsive manifestations.

However, the decerebrate cats did have heaving respiratory movements involving the upper extremities. These were described also by Bean in the aforementioned study and by Behnke (1934), who referred to them as "respiratory seizures" ultimately related to edema and hypersecretion in the respiratory passages causing pulmonary difficulty. Gersh's conclusion was that the seizures of hyperoxic convulsions "originated" in the cerebral cortex and that the cerebral cortex as a whole was the site of origin of the motor seizure. Some evidence was obtained by Stein and Sonnenschein (1950), by placing electrodes over the cerebrum and cerebellum and recording simultaneously, that may indicate that hyperoxic convulsions may start elsewhere than in the cerebral cortex and only spread there

secondarily. That any of these conclusions are justified remains unconfirmed.

Then we have the interesting recent work of Batini, et al (1953), in Italy, working with cats breathing high partial pressures of oxygen. They found after acute or chronic removal of the motor cortex, or after medullary pyramidotomy, that hyperoxic convulsions were abolished on the contralateral side; the seizures also being absent unilaterally when the animal was anesthetized with urethane, but when unanesthetized slight unilateral clonic movements were observed. In a "pyramidal" preparation (a cat who has sustained an extensive thermolytic destruction of almost all ascending and descending pathways at the level of the mesencephalic tegmentum, leaving the basic pedunculi intact), normal intensities of convulsions were observed. They conclude that the fits are pyramidal in origin, and that extrapyramidal contributions are very small or altogether absent. Batini, et al (1953) have also done a few experiments attempting to correlate the EEG patterns of hyperoxic convulsions with recordings from electrodes situated in several subcortical structures. They found that the epileptic waves appeared simultaneously in the frontal, parietal, and occipital cortices. Not infrequently, however, the subcortical epileptic waves, as recorded from the caudate nucleus and intralaminar thalamic nuclei, appeared with a certain delay (of some minutes on occasion) and were less extensive than those in the cortex. Because of the limited number of subcortical structures investigated and the small number of animals used, no conclusions were drawn regarding neurophysiological mechanisms.

SUMMARY

This is approximately all the literature holds for those interested in this aspect of oxygen toxicity, and it is immediately apparent that before any of the data can be accepted, they must be confirmed. Also, before any data can be made to fit any sort of pattern purporting to explain seizure mechanisms, much more remains to be done.

How then shall we attack this monster about whom we know so little neurophysiologically? Let me say at this point, in no uncertain terms, that it should be readily apparent to everyone here that the basic problem of oxygen toxicity in man from a therapeutic and preventative standpoint is not a neurophysiological one and that measures to alleviate the condition as a threat to those engaged in work exposing them to high partial pressures of oxygen must take precedence in a program of applied research which must progress along lines designed to identify and irradicate the neural insult.

CONCLUSIONS

I believe the neurophysiologist must first train his guns with the aid of the anatomist. As I stated earlier, it is essential to define better the site or sites of convulsive activity. The conflicting testimony of the several investigators working with extirpation preparations tells us that this goal is elusive, but I do not believe it is unreachable. In our own laboratory, Dr. Perot, who has worked with

me on and off for several years, even donning uniform to follow me in the Navy, and I are preparing to explore the entire brain serially from stem to stern with multiple electrodes in gridiron fashion. Should we be successful in finding a focus or foci, we may be able to use the information to build a platform for attacking the problem of neuronal spread through the central nervous system. This program, neurophysiologically speaking, is a meager one, but represents a prodigious amount of planning and preparation and an even greater amount of contemplated labor. I only mention this to emphasize the need for recruitment of others working in the field of neurophysiology, others who conceivably can be stirred to take an interest in this problem if the fundamental nature of the question is more widely publicized. This is brought home to me fairly frequently and vividly as when recently a colleague of mine inquired about the work in which I was presently engaged. I had no more than mentioned hyperoxic convulsions when the blank expression I have long ago learned to expect appeared on his face. This expression quickly changed to one of complete disinterest when I explained weakly that hyperoxic convulsions were encountered in diving personnel and underwater swimmers. To him this was strictly a military problem, one to engage the interest of a few, a few who would condescend to tackle a very specialized problem in applied research. It takes some educational effort to bring about a better comprehension regarding the "sameness" of the hyperoxic convulsion question and the question of mechanisms of epilepsy and other convulsive phenomena.

If I have thrown a "monkey wrench" into your thinking machinery regarding the importance of the neurophysiological approach to the solution of the hyperoxic convulsion problem, I apologize. But if I have in some way conjured up a better understanding for you of the magnitude of the neurophysiologist's difficulty, or uncovered a latent desire within you to help solve one of the most interesting as well as one of the most challenging of mysteries known to man, I feel indebted for the time made available for this presentation.

2.5 RESPIRATORY AND CIRCULATORY ACTIONS OF HIGH OXYGEN PRESSURE

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OXYGEN TOLERANCE

Studies of the tolerance to oxygen of normal men have made it quite clear that oxygen toxicity can express itself in at least one of two ways. If oxygen is breathed for prolonged periods at 1 atmosphere, a mild pulmonary irritation may develop in 14 to 24 hours of continuous oxygen breathing. This phenomenon has as yet no importance in diving since it has not been encountered in the much shorter periods which man is able to endure under water. It is also well known that at increased ambient pressure the tolerance to oxygen decreases sharply with increasing depth, as illustrated in Figure 2.5-1, which is constructed from data obtained at the Experimental Diving Unit. This figure shows the relationship between the diving depth or ambient pressure in atmospheres and the time required to develop symptoms of oxygen toxicity in a dry pressure chamber. It can be seen that at 60 feet of sea water in the dry chamber none of the twenty subjects exposed to oxygen breathing developed symptoms in the two-hour time limit of the exposure. At 80 feet 50 per cent of the subjects had developed symptoms in about 60 minutes and at 100 feet 50 per cent of the subjects had developed symptoms in 25 minutes. It is also evident from Figure 2.5-1 that even when oxygen toxicity does occur, its time of onset is variable in different individuals. The work of Donald stresses variability of the safe latent period even within an individual studied at different times. Few studies of this nature have been carried out during the actual performance of work under water.

Figure 2.5-2 summarizes a number of such studies also carried out at the Experimental Diving Unit, and Dr. Lanphier will present later a more recent attempt to define the limits of tolerance to oxygen in underwater swimming. For our present purposes it will suffice to point out that work, for an as yet unknown reason, decreases the tolerance to oxygen. While work at depths less than 30 feet has not produced symptoms of oxygen toxicity in the maximum times thus far studied, the tolerance to oxygen during active underwater swimming becomes sharply less at depths greater than 30 feet.

CARBON DIOXIDE AND OXYGEN TOXICITY

It is my intention today to concentrate primarily upon the effects of oxygen breathing at high partial pressure upon carbon dioxide transport and upon the relationships of carbon dioxide to oxygen toxicity.

The probability that carbon dioxide contributes to the toxicity of oxygen has been disturbingly well supported for about 30 years. The concept originated with Gesell, who proposed that at high pressures of inspired oxygen it should be possible to force enough oxygen in physical solution in the arterial blood to meet the demands of tissue metabolism. In this event homoglobin should be chemically inacti-

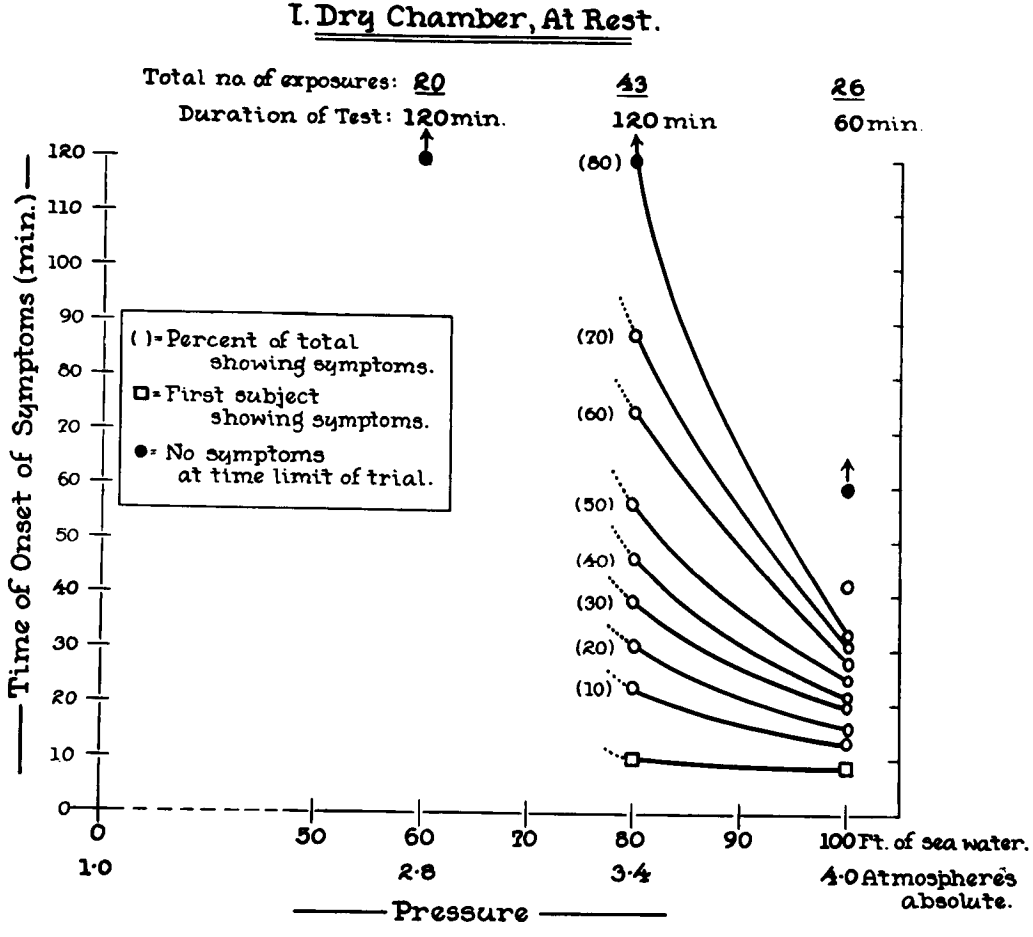

Figure 2.5-1 Development of Oxygen Toxicity in Dry Chamber at Rest. (Graph prepared for protocols of data obtained at U. S. Naval Experimental Diving Unit, Washington, D. C., Project X-337 (Sub. No. 62, Report No. 1, January 1947), "Symptoms of Oxygen Poisoning and Limits of Tolerance at Rest and at Work", O. D. Yarbrough, W. Welham, E. S. Brinton, and A. R. Behnke)

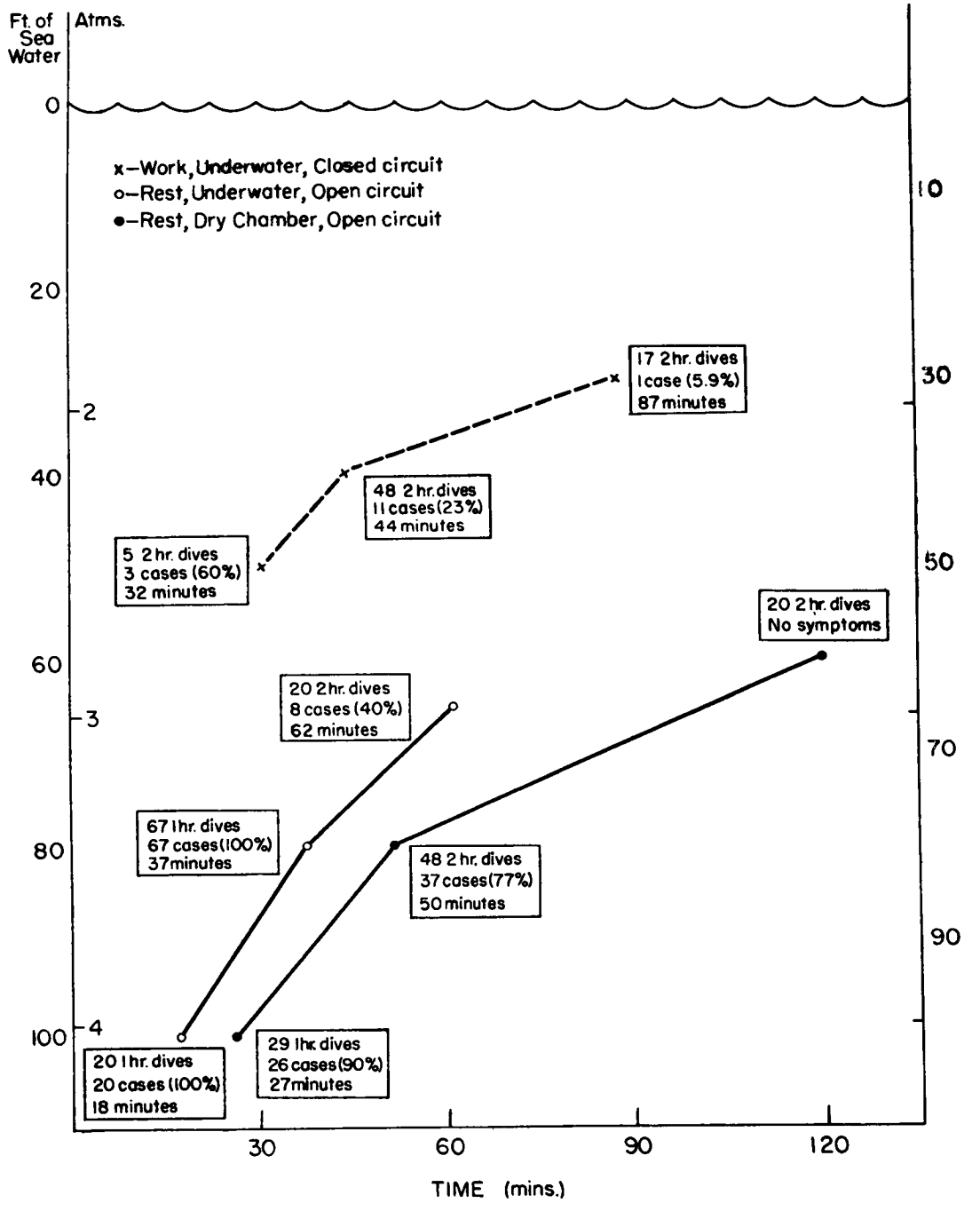

Figure 2.5-2 Effect of Work Under Water Upon Oxygen Tolerance

vated by the excess oxygen tension and no longer function or be important in oxygen transport. Oxyhemoglobin would therefore circulate through the tissues unchanged. The consequent interference with hemoglobin reduction and consequent failure of release base from hemoglobin for transport of carbon dioxide caused Gesell to conjecture an accumulation of carbon dioxide in the tissues as a contributory or causative factor in the symptomology of oxygen toxicity.

Gesell's hypothesis of a severe carbon dioxide autointoxication has over the course of time been supported by several kinds of experimental evidence. The studies of Campbell, Taylor, and of others, who have attempted to measure changes in tissue pCO_2 by repeated analysis of the percentage of carbon dioxide in subcutaneous gas depots, appear to show an extreme elevation of depot carbon dioxide on exposure of the animals to high oxygen pressures. Typical results of these experiments are shown in Figure 2.5-3. It should be noted that the rise in carbon dioxide

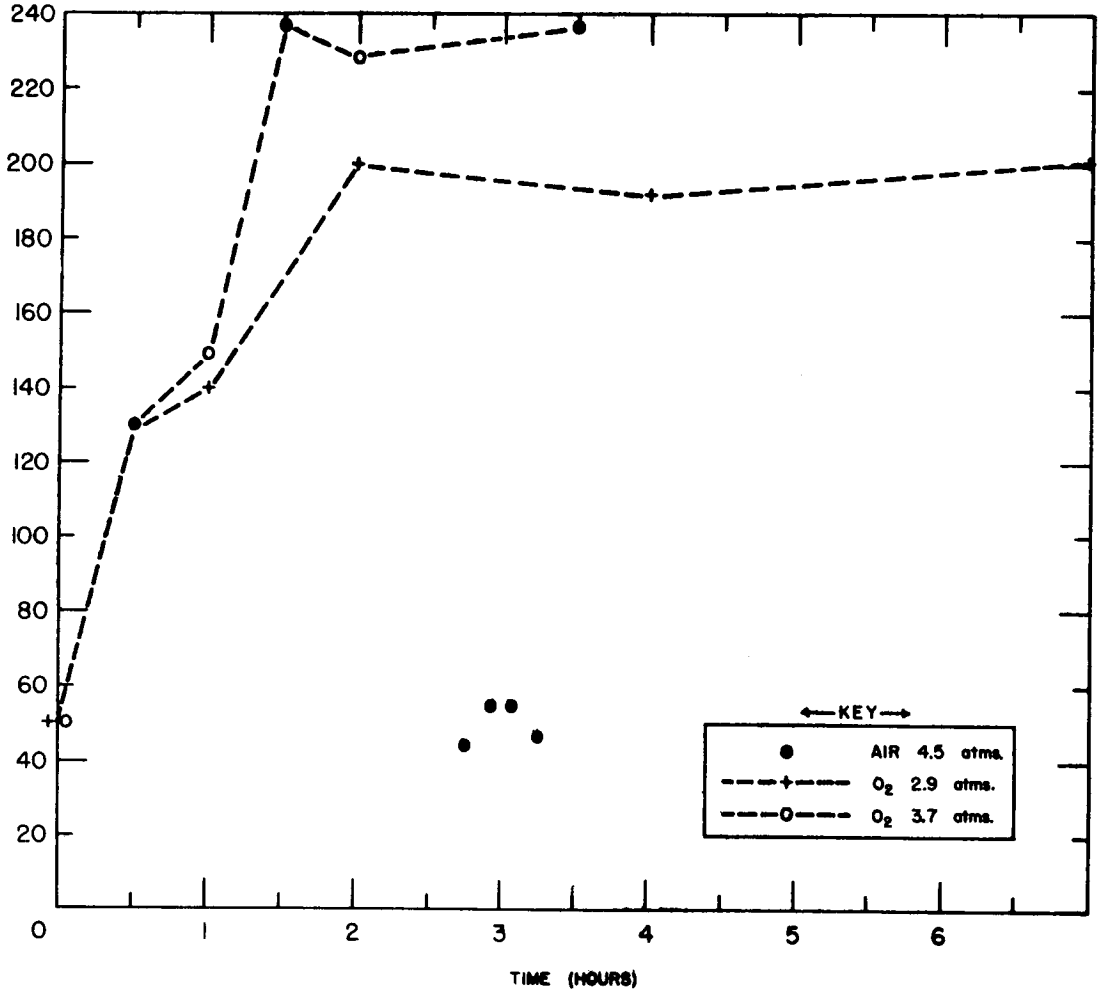

Figure 2.5-3 pCO_2 of Subcutaneous Gas Depots in Cats Breathing Oxygen or Air at Increased Ambient Pressures (after H. J. Taylor, J. Physiol. 109:272, 1949)

tension is shown as occurring early, much before the onset of oxygen convulsions in the small animals used. In this instance the animals were cats which convulsed in approximately 3 hours of exposure to oxygen at the pressures employed. Control cats exposed to air at the same pressure did not develop the same high depot carbon dioxide tensions.

A second type of experimental evidence supporting Gesell's concept of an accumulation of a carbon dioxide factor in oxygen toxicity is the demonstration by Leonard Hill, and others after him, who showed that inhalation of carbon dioxide with oxygen at high pressure markedly shortens the latent period of oxygen toxicity. This is where the situation stood about two years ago when a group of us in the Department of Pharmacology at the University of Pennsylvania began studies of blood gas transport during oxygen breathing at increased ambient pressure, i.e., a logical hypothesis by Gesell supported by two main types of experimental evidence. Objectors to Gesell's concept were Behnke and his co-workers, who did not find the same high carbon dioxide tensions in the venous blood of a dog exposed to oxygen breathing at 3.8 atmospheres. Nor did Stadie and Haugaard find that the addition of carbon dioxide to oxygen facilitated the depressant effect of oxygen upon respiration of brain tissue slices at high pressures.

Our own studies were initiated in order to obtain answers to several questions bearing upon the physiological effects of oxygen and upon oxygen toxicity. These questions were as follows:

1. Does oxygen cause a massive rise in tissue carbon dioxide tension in man? (For this study we used the brain as the tissue, employing internal jugular venous blood rather than gas depots as an index of changes in tissue carbon dioxide tension.)

2. Does oxygen at high partial pressure cause a severe constriction of cerebral blood vessels?

3. Does oxygen at high pressure decrease the rate of oxygen consumption of the human brain?

4. Is there a measurable decrease in carbon dioxide output during oxygen breathing at high pressure?

The methods employed for these studies were essentially those which would be employed in performing measurements of blood gases, respiration, and cerebral circulation in a sea-level laboratory, with the modifications necessary to permit their employment at increased ambient pressures.

Figure 2.5-4 summarizes the average data obtained in a series of studies in young, normal men breathing oxygen at 3.5 atmospheres. The figure shows that, as Gesell predicted, the addition of oxygen in physical solution did decrease the reduction of hemoglobin in the brain capillaries. The amount of oxygen added in physical solution at 3.5 atmospheres was approximately 6.5 volumes per cent. This is somewhat in excess of the normal cerebral arterial venous oxygen difference of about 6.1 volumes per cent obtained in the subjects during air breathing at sea level. Because of a decrease in cerebral circulation, this amount of physi-

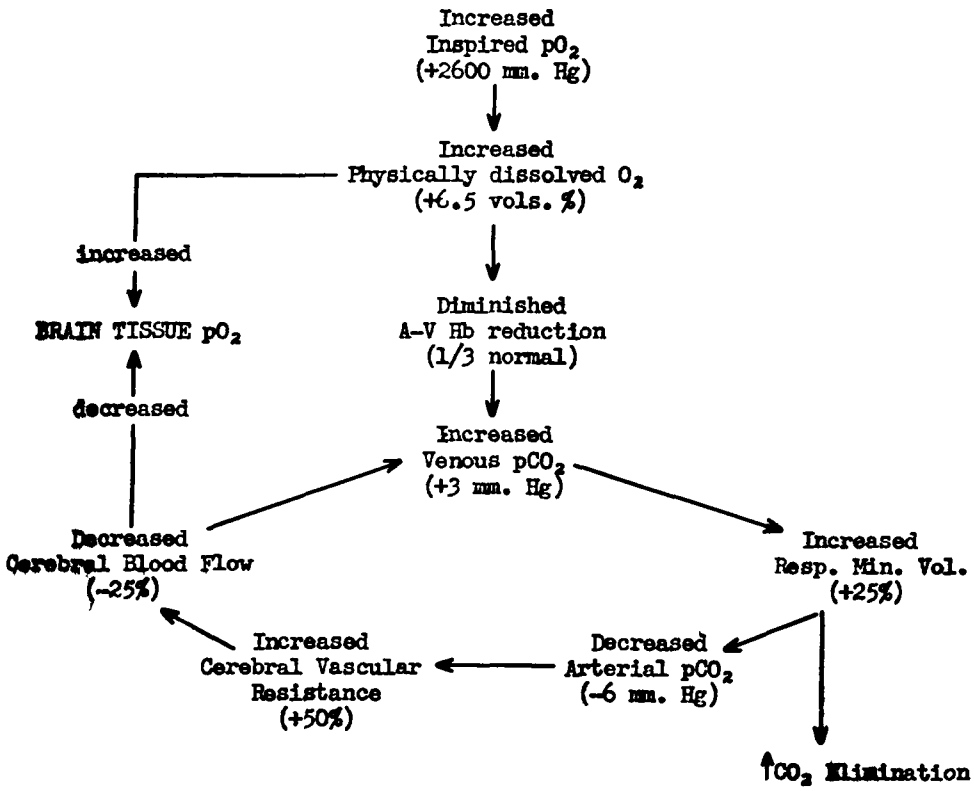

Figure 2.5-4 Effects of Oxygen Breathing at 3.5 Atmospheres (Average Findings in Normal Men)

cally dissolved oxygen was not actually sufficient to prevent reduction of hemoglobin entirely. About 60 per cent of the normal hemoglobin reduction was prevented however. A rise in venous carbon dioxide tension and acidity did occur, but these changes were small, averaging 3 mm Hg and 0.03 pH units respectively.

While these results qualitatively verify Gesell's concept of a retention of carbon dioxide in the tissues, it would appear that if venous pCO_2 is a useful index of tissue carbon dioxide tension, no gross elevation of brain pCO_2 occurred in our subjects. The average 3 mm rise in carbon dioxide tension in cerebral venous blood is smaller than the rise reported as occurring in small, experimental animals. It is actually only about 1/100 of that reported by Taylor as occurring in cats exposed to approximately the same oxygen pressures. Moreover, in our subjects the elevation of central pCO_2 appeared to be the most likely cause of an increased respiratory stimulation, lowered arterial pCO_2, increased cerebral vascular resistance, decreased cerebral blood flow, and thus presumably resulted in a brain tissue oxygen tension lower than that which would have existed if cerebral vasoconstriction had not occurred. This sequence of events suggests that carbon dioxide accumulation in the brain tissue, rather than aggravating the effects of the toxicity of oxygen, may actually increase oxygen tolerance by lowering the effec-

tive oxygen tension in brain tissue. This then would be in direct opposition to Gesell's concept of a contributory role of carbon dioxide in oxygen poisoning.

What then of the very high (200 to 300 mm Hg) pCO_2 levels reported as occurring in small animals exposed to high oxygen pressures? Figure 2.5-5 shows the results of our repetition of experiments involving equilibration of subcutaneous gas depots and analysis of carbon dioxide concentrations in subcutaneous gas depots in rabbits. The figure shows that regardless of the injected carbon dioxide tension, the pCO_2 of the gas depot promptly fell to levels close to those expected in arterial blood. Essentially similar results were obtained in man, cats, and dogs. Only after the time required for development of oxygen toxicity did the depot pCO_2 rise to high levels. This rise was found in rabbits, cats, and dogs to be associated with the respiratory failure of terminal oxygen toxicity since the pCO_2 rise occurred in arterial blood as well as in venous blood and subcutaneous depots. Reasons for considering that earlier experiments of this nature were technically incorrect have been published. The very high subcutaneous gas depot carbon dioxide tensions previously reported appear to have been due almost entirely to errors in technique, such as decompressing the animals before withdrawal of samples for subsequent analysis, and no longer deserve consideration as evidence supporting an important role of carbon dioxide in oxygen poisoning.

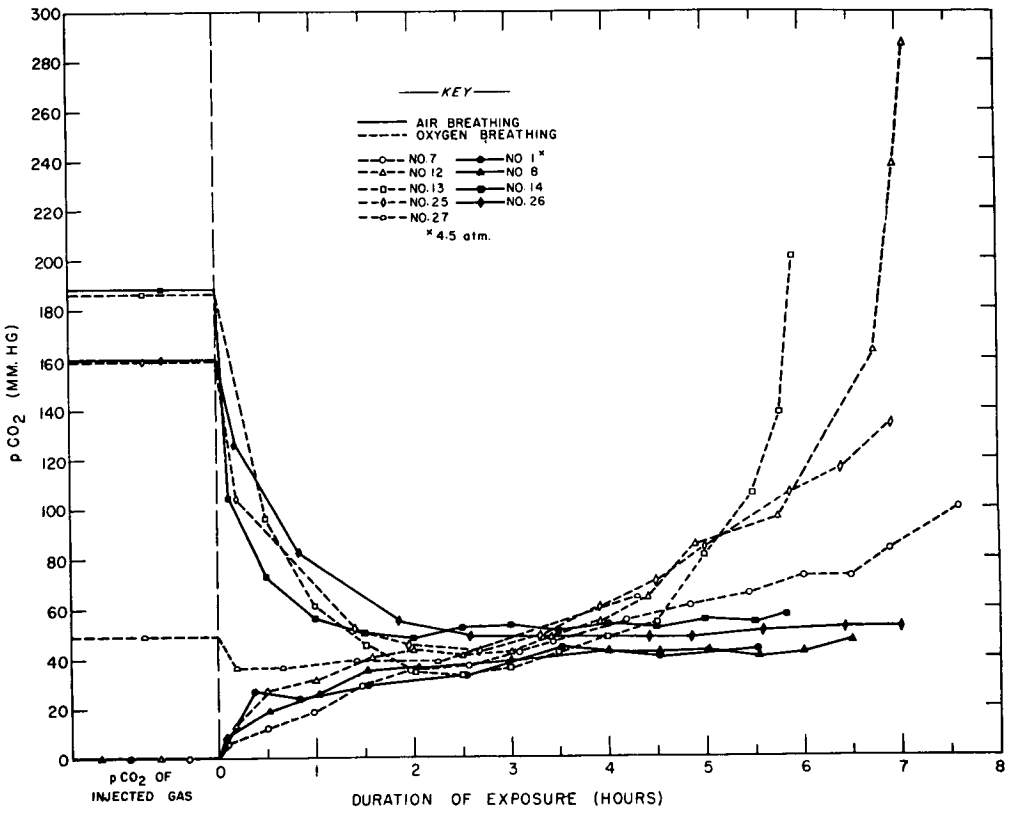

Figure 2.5-5 Carbon Dioxide Tension in Subcutaneous Gas Depots in Rabbits During Prolonged Exposure to Air or Oxygen at Increased Ambient Pressure

There remains, however, the unchallenged ability of carbon dioxide added to oxygen inspired at increased pressure to shorten the latent period of oxygen toxicity. Carbon dioxide in this case is added not from the tissue side, but to the arterial blood by inhalation of carbon dioxide at supranormal tensions. We have studied this phenomenon in human patients being studied for possible therapeutic effects of oxygen, as in the convulsive treatment of schizophrenia. After measuring the oxygen tension in arterial and cerebral venous blood during the inhalation of oxygen at 3.5 atmospheres, 2 per cent carbon dioxide was added to the oxygen breathed and blood samples were again taken. Figure 2.5-6 shows the effects of adding carbon dioxide to inspired oxygen at increased ambient pressure upon the arterial and internal jugular venous blood oxygen tensions. During air breathing at sea level, arterial blood enters the brain with an oxygen tension of about 100 mm Hg and leaves with an oxygen tension of about 40 mm Hg. When oxygen is breathed at 3.5 atmospheres and arterial pO_2 is therefore raised to about 2000 mm Hg, a fall of nearly 2000 mm Hg occurs as blood perfuses brain tissue, with the result that venous blood draining from the brain has an oxygen tension only slightly higher than that during air breathing at sea level. The addition of 2 per cent carbon dioxide to the oxygen at 3.5 atmospheres does not change significantly the arterial pO_2. On the other hand, cerebral venous pO_2 is raised nearly 1000 mm Hg by carbon dioxide breathing. A most likely cause of this great elevation in venous pC_2 is a cerebral vasodilatation by the increased arterial carbon dioxide tension. Certainly in the face of such a massive rise in venous oxygen tension, brain tissue oxygen tension must have been increased. It would therefore appear that one important mechanism by which carbon dioxide inhalation can shorten the latent period of oxygen poisoning has been demonstrated, namely, that the addition of carbon dioxide to oxygen increases the dose of the toxic agent in brain tissue or increases the number of cells exposed to the toxic tensions of oxygen.

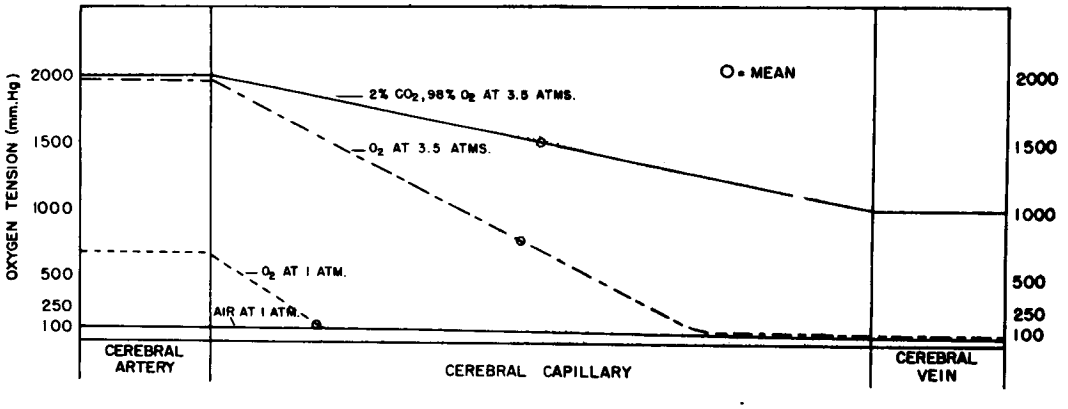

Figure 2.5-6 Arterial and Internal Jugular Oxygen Tensions in Man

It now becomes necessary to consider two possible roles of carbon dioxide in oxygen toxicity. First, as a consequence of an increase in carbon dioxide in the tissues brought about by interference with carbon dioxide transport, carbon dioxide may cause hyperventilation and hypocapnia, cerebral vasoconstriction, and a lowering of brain tissue pO_2, thus minimizing oxygen toxicity. A second role, increased arterial pCO_2, occurring during carbon dioxide breathing, re-inhalation of dead space air, breath holding, or inadequate alveolar ventilation, may cause cerebral vasodilatation and a great rise in brain tissue oxygen tension, increasing the toxicity of a given tension of inspired oxygen. It remains possible that carbon dioxide itself may exert some effect upon brain tissue enzyme systems and contribute to oxygen toxicity by a mechanism other than the alteration of level of pO_2 in the tissue. Such an effect of carbon dioxide has not yet been demonstrated.

EXERCISE AT HIGH OXYGEN PRESSURES

The next area of high oxygen physiology we have approached is that of exercise which, as previously mentioned, shortens the latent period of oxygen toxicity. In the studies now in progress we are attempting to measure the relationships between respiratory changes and blood gas composition on the arterial and venous sides of the cerebral circulation. Studies are performed during exercise while breathing air at 1 atmosphere and during exercise at 2 atmospheres of oxygen pressure. Figure 2.5-7 shows in one of our subjects the increase in ventilation produced during exercise while air breathing at sea level and the effect upon this ventilation of oxygen breathing at 2 atmospheres. The corresponding changes in arterial pCO_2, bicarbonate, and pH are also shown. The changes shown in this one subject are characteristic of the group thus far studied. The expected increase in respiratory minute volume produced by exercise at sea level is associated with a fall in arterial carbon dioxide tension. The marked decrease in plasma bicarbonate and pH in spite of the fall in arterial pCO_2 indicates the addition of fixed acids to the blood. In effect there is a concurrent metabolic acidosis with partial respiratory compensation. The breathing of oxygen at the same level of exercise lowered the ventilation and secondarily increased arterial pCO_2. Apparently the higher content of oxygen in arterial blood at 2 atmospheres pressure facilitated the oxidation of fixed acids in the working muscles and decreased their spillage into the circulating blood. This is indicated by the partial return of plasma bicarbonate towards the resting level and the increase in arterial pH in spite of a rise in arterial pCO_2. Oxygen has apparently removed, diminished, or depressed a respiratory drive in this subject. The nature of the drive affected is not yet known.

Simultaneously with these measurements, similar determinations were made on samples of blood obtained from the internal jugular vein. It was hoped that these measurements, shown in Figure 2.5-8, might provide a clue to possible relationships of "central" levels of carbon dioxide tension and pH to the respiratory response in exercise. The venous data also show that the fall in respiratory minute volume on administering oxygen to an exercising subject at 2 atmospheres occurs in spite of a gross elevation in blood pCO_2, which actually proves to be secondary. As striking is the associated increase in acidity of venous blood. It would appear that neither carbon dioxide nor pH of blood can be considered important factors in the respiratory control of exercise. The relationship of these studies to the known decreased tolerance to oxygen during exercise is not yet clear. In certain subjects a marked depression of respiration was associated with a consid-

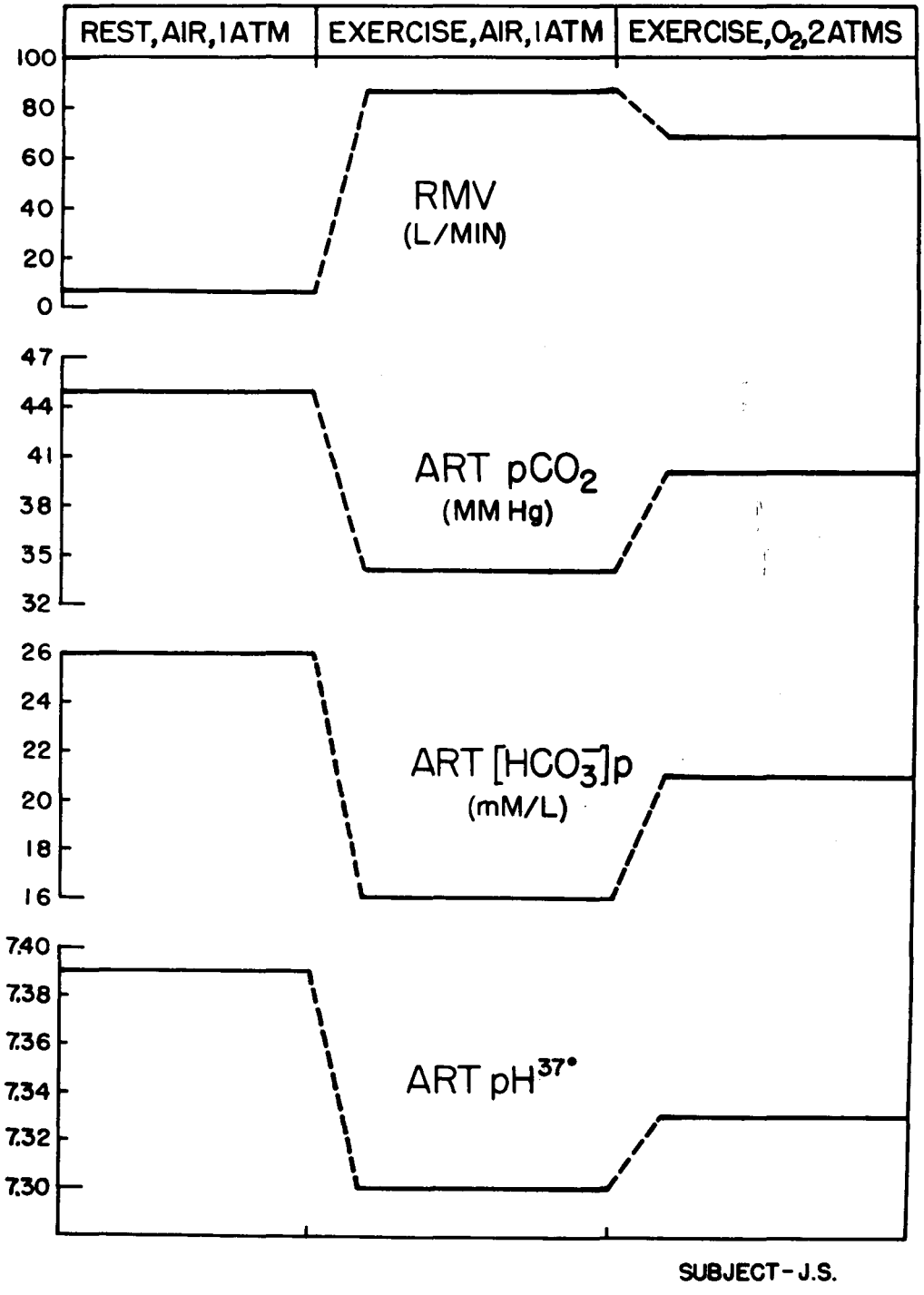

Figure 2.5-7 Relationships of Arterial pCO_2, pH, and Bicarbonate to Respiration During Exercise Breathing Air at 1 Atmosphere and Oxygen at 2 Atmospheres

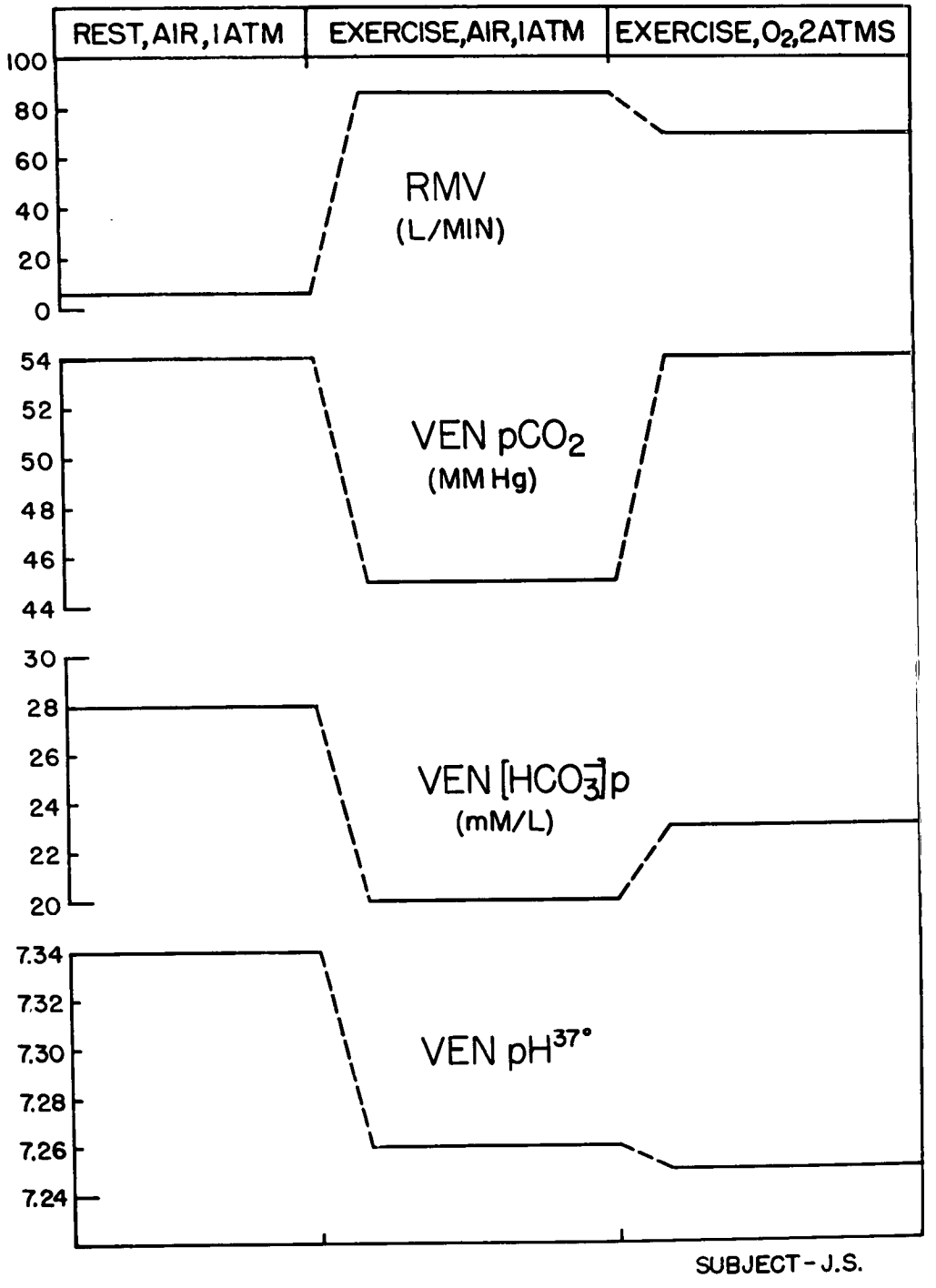

Figure 2.5-8 Relationships of Cerebral Venous pCO_2, pH, and Bicarbonate to Respiration During Exercise Breathing Air at 1 Atmosphere and Oxygen at 2 Atmospheres

erable increase in arterial pCO_2 above normal. It is quite possible that in certain subjects, very sensitive to respiratory depression by oxygen during exercise, a phenomenon similar to that produced by carbon dioxide inhalation would elevate brain tissue carbon dioxide tension. We have been unable to demonstrate this in more than a few subjects, and then only to a degree much smaller than that produced by carbon dioxide inhalation. It is perhaps significant that on the average no change in cerebral blood flow is brought about by either exercise alone or exercise with the inhalation of oxygen at 2 atmospheres in these studies.

INTERMITTENT EXPOSURE TO HIGH OXYGEN PRESSURES

One of the most interesting studies of oxygen toxicity in which we have been involved is one aimed at determining the effects of intermittent exposure to oxygen inhalation at several atmospheres pressure. Field experience indicates that successive dives are possible, breathing oxygen to the limits of oxygen tolerance, at intervals of a week, a day, and presumably within a few hours, without cumulative effects. Naval interest in self-contained diving has now generated requirements beyond the physiological barriers raised by oxygen toxicity and bends (necessity for slow decompression). If oxygen toxicity develops slowly, as indicated by the very long latent period at moderate pressures, and is rapidly reversed on lowering oxygen tension, as also appears to be the case, an alternation of high and low tensions in the respired air might conceivably greatly extend the working time at increased ambient pressure. Field experiments of this sort were carried out during World War II, and we are now involved in experiments with small animals aimed at determining the minimum interruption of oxygen breathing which will restore tolerance to oxygen at increased pressure. Figure 2.5-9 illustrates a schedule which we have used with guinea pigs in studying this problem.

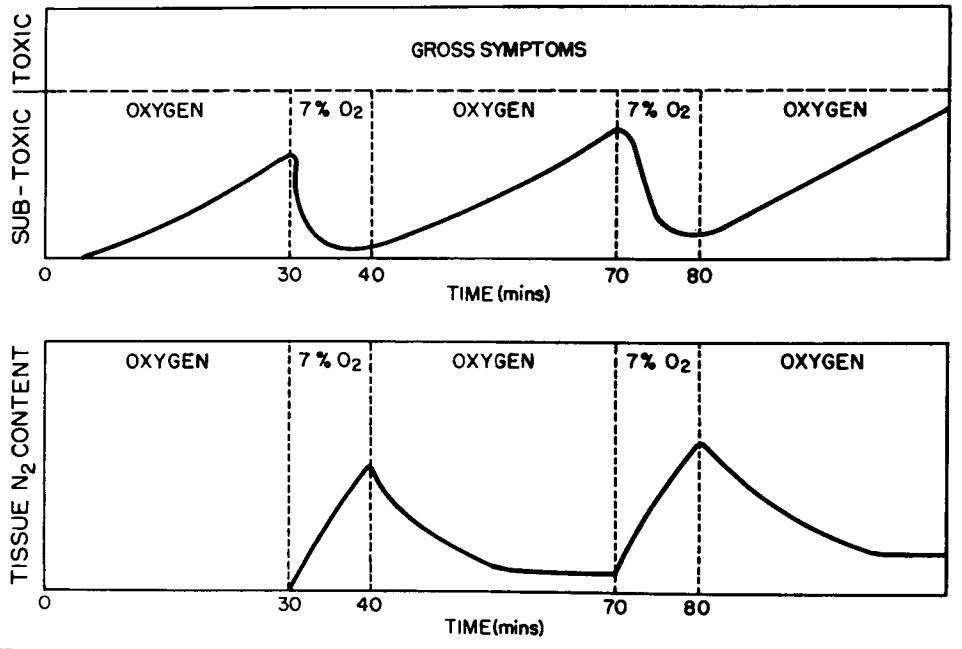

Figure 2.5-9 Rationale of Intermittent Exposure to High Oxygen Pressure

At 3 atmospheres ambient pressure control groups of guinea pigs were exposed to 100 per cent oxygen continuously. A second group of guinea pigs received 100 per cent oxygen to breathe for thirty minutes, then 7 per cent oxygen (equivalent to 21 per cent at 1 atmosphere) for ten minutes, 100 per cent oxygen for thirty minutes, and repetitions of this cycle for the duration of the experiment. In the group of animals exposed to high oxygen pressures intermitten' y, nitrogen elimination occurs during the oxygen breathing period and nitrogen absorption during the short periods of breathing the low-oxygen mixture. If the amount of nitrogen taken up is such that nearly complete elimination of that nitrogen can take place during the succeeding period of oxygen breathing, bends should not be encountered on ultimate decompression of the animals. Moreover, if the latent period of oxygen toxicity is not exceeded and any return of oxygen tolerance occurs during the exposure to low-oxygen mixtures, oxygen toxicity should not develop as rapidly as when oxygen exposure is continuous. The results of exposing guinea pigs to the schedule described are shown in Table 2.5-1. This table shows that while the group of

	Time of Exposure in Hours		
	Continuous	Intermittent	
		O_2 Exposure	Total Time
First Signs of O_2 Toxicity	4.1	14.0	18.7
Toxicity present in 50% of Animals	4.8	15.3	20.3
Mean Time for Development of Toxicity	5.9	16.6	22.0

Table 2.5-1 Time of Appearance of Oxygen Toxicity Symptoms During Continuous and Intermittent Exposures to High Oxygen Pressure in Guinea Pigs

guinea pigs exposed continuously to oxygen showed the first signs of poisoning at 4.1 hours (mean time, 5.9 hours), the intermittent group began to develop oxygen toxicity only after an oxygen exposure of 14 hours, and two of the animals exposed had not done so at the end of the 25-hour period of the experiment. Evidently even a 10-minute interruption of oxygen breathing allows a partial return of oxygen tolerance although it does not completely prevent the development of oxygen poisoning in a 25-hour exposure at 3 atmospheres. The results further imply that under these conditions the rate of recovery from oxygen poisoning exceeds the rate of development. Bends was not encountered in the two animals which survived the 25-hour exposure. Previous studies indicate that a 5-minute interruption of oxygen breathing does not produce a significant protection against oxygen toxicity, but that a 15-minute interruption does offer protection. It would appear that 10 minutes are close to the minimum which will produce a practical extension of oxygen tolerance, and it is quite possible that a further slight increase in the

interruption of oxygen breathing may have a marked effect upon tolerance to oxygen.

At a time when the use of mixtures of oxygen with inert gases is not clearly the answer to increasing diving time and depth, it is possible that some practical alternation of oxygen, oxygen-nitrogen, oxygen, oxygen-helium can be devised with a sequence aimed not only at extending diving duration by minimizing oxygen toxicity, but also by minimizing the need for slow decompression by permitting the elimination of inert gas in the act of extended diving operations. Dr. Behnke will undoubtedly consider the possibility of oxygen breathing during ascent following self-contained diving with inert gas-containing mixtures as a means of reducing the incidence of bends.

2.6 PANEL-FLOOR DISCUSSION OF OXYGEN TOXICITY

Dr. C. J. Lambertsen, Chairman
Dr. J. Bean
Dr. N. Haugaard
Dr. K. E. Penrod
Dr. S. Stein

DR. LAMBERTSEN: I would like to ask Dr. Bean how he produces the motor paralysis in rats. I have known of the paralysis as described by Dr. Bean for many years, but we have not seen it, either in small animals, rats, guinea pigs, rabbits, cats, or in human subjects who have been exposed to oxygen convulsions as many as ten times. Could you describe your production of these paralyses?

DR. BEAN: The reason for exposing these animals originally was to see whether an additive effect of repeated exposures could be achieved. We found that if these rats were exposed to oxygen at from approximately eighty pounds pressure, absolute, to a point where they would be convulsed and then decompressed with care to prevent embolism or bubble formation over a period of time, these paralyses would gradually occur, increase in severity and be permanent. We have had exceptions because some animals are very resistant to oxygen; there is a very great individual varying of susceptibility.

DR. LAMBERTSEN: In other words, it takes many exposures.

DR. BEAN: That is right.

DR. LAMBERTSEN: Over how long a period?

DR. BEAN: There is a great individual variation in that too; some of them have been exposed for a matter of weeks, as many as forty or fifty times; others, fewer times. The occurrence of oxygen convulsions apparently is not essential to the precipitation of these effects.

DR. LAMBERTSEN: So that is it. Our reason for not having run into the permanent paralysis ourselves is that in man we would go no higher than about ten convulsions, whereas you have given far more in the small animals. We probably would have found them if we had continued our exposures to the same extent.

DR. BEAN: I should think so. I would hate to commit myself as to how man would react because there appears to be a great difference in the variation, not only from individual to individual, but between species also.

DR. LAMBERTSEN: I would like to ask Dr. Haugaard if he has any idea of whether the drug, Bal, or British anti-Lewisite, would possibly be a useful drug for blanketing the SH groups that he has talked about this morning as being susceptible to oxygen poisoning.

DR. HAUGAARD: Yes, I think that would be an important drug to study from that point of view. I know of no work using it now, but I do think that it would be a drug to try.

DR. PENROD: I tried that in 1948 with no success whatsoever.

DR. LAMBERTSEN: Could you elaborate a little on your reasons for wanting to try it?

DR. PENROD: For precisely the same reasons developed here. The SH theory was put forth at about the same time Bal had been produced as a possible protectant of this SH group, so it seemed to be a natural compound to try. In a preliminary series run on rats only, no protection was observed.

DR. LAMBERTSEN: Was protection indicated by occurrence or absence of convulsions?

DR. PENROD: That and survival -- both criteria.

DR. LAMBERTSEN. Dr. Stein, I should like to ask about the changes in brain potential during oxygen breathing as indicated by the Davis and Brink oxygen electrode. Both Gersh, and Stein and Gerard found on exposing small animals to oxygen at 1 atmosphere a given electrical potential was obtained. When the oxygen pressure was increased to several atmospheres, a major spike was observed to occur which exceeded the value obtained at 1 atmosphere by as much as fifty-fold and then fell to nearly normal levels in spite of continued exposure of the animals to high levels of oxygen breathing. Would you comment on this?

DR. STEIN: Yes, I will. I would like to state that the increase in oxygen tensions, as recorded by the Davis and Brink device, never showed a rise unless the oxygen level reached 2-1/2 atmospheres. We interpret that to mean that below these pressures we were not getting a toxic concentration at the tissue level.

Taking some of Dr. Desoille's and Dr. Bean's work to task, we asked ourselves whether or not this represented a carbon dioxide function. If the hemoglobin were capable of carrying carbon dioxide only up to a certain level, then broke off, where did the transport system break down? We thought that perhaps it might break down when the dissolved oxygen in the plasma reached a level capable of maintaining metabolism. Simultaneously, of course, at that level if the hemoglobin were unable to pick up the carbon dioxide, we would have local accumulation at the tissue level.

Regarding the fall which came invariably after the onset of seizures, we have never been able to give ourselves or anyone else an adequate explanation. This, I think, might be explained on the basis of an enzymatic disruption, if you will. I am not sure. It may be in the SH grouping; it may be in some other enzyme or coenzyme system that we are unable to study because of our lack of technical knowledge.

DR. LAMBERTSEN: Do you think it truly represents a massive, sudden, and temporary rise in oxygen tension in brain tissue?

DR. STEIN: Yes, I do, if the electrode as we have used it, calibrated against pure solution, is an oxygen electrode. I have no reason to believe it is not. If you think of other oxidizing substances that might be present, you come up with a blank. We have tried to think of numerous substances that might act on these electrodes to give us such a reading.

DR. LAMBERTSEN: Did not Brink mention hydrogen peroxide?

DR. STEIN: Yes, he did. If you put an electrode in a solution and add hydrogen peroxide to the solution, you get a rise, but if you then measure the content of the solution for oxygen, you find that you have an oxygen concentration much higher than that which would be represented in the tissue preparation. Now it is conceivable, of course, that hydrogen peroxide or other peroxides could exist in the tissue and not break down and affect the electrode, but then we have to ask ourselves the question, "Why, in the in vitro preparation, the check preparation, do we get so much oxygen, not a recoverable quantity that will equal that which we found as a measure in our tissue?"

That does not mean that we will not accept the presence of peroxide or peroxides as causing the rise in the electrode. We just have not been able to demonstrate it to our own satisfaction.

Perhaps Dr. Haugaard can give us a little help on that, too.

DR. HAUGAARD: I would say that the presence of catalase in the tissue would be a factor against the accumulation of hydrogen peroxide. This enzyme is found in almost every cell of the body.

DR. STEIN: We have never been able to pick up the peroxides per se.

DR. RAHN: I wonder whether your theory would explain this drop that you have observed, if it is not an artifact, because it would require first a rising in the oxygen tension, and then the various reactions you have demonstrated which would bring down the oxygen tension. Is that true or not? I do not know the time course of these events.

DR. LAMBERTSEN: There is where the difficulty lies, Dr. Rahn. The spike would occur about 10 or 15 minutes following compression to a pressure of about 8 atmospheres. Shortly after this would follow the onset of convulsions. Is that so, Dr. Stein?

DR. STEIN: Yes. As a matter of fact it is coincident with the peak, or occasionally just before the peak, but around the rise of the curve.

DR. LAMBERTSEN: Our experiments in man were what might be called steady-state experiments in which you produce the situation desired. Figure 2.5-6 reproduces one of the diagrams illustrating the oxygen tensions on the arterial and venous sides of the cerebral circulation. These are the values we are measuring. Between them is just space representing a brain capillary. After ten or fifteen minutes of oxygen breathing at high pressure, we find several thousand millimeters of oxygen tension in the arterial blood. It takes a matter of just a few

minutes to achieve that, the washout time of the alveoli, so that that time is certainly within the time scale for the appearance of the spike.

It takes one circulation time across the brain for the fall from 3000 mm to somewhere around 70 on the venous side, so that is a matter of a few seconds. I do not really see a slow buildup to one situation with a change to a different one, but rather an attainment of a steady balance state.

DR. RAHN: Do we not need the reduced cerebral blood flow to get the oxygen down as you measured? In order to get the cerebral blood flow down you have first to excite the respiratory center with the carbon dioxide, which lowers the arterial carbon dioxide and all of which takes time.

DR. LAMBERTSEN: Yes, if you did not have that sort of cycle, you might end up with a double cerebral blood flow, such as one gets with 3 per cent carbon dioxide. Say this is 100 per cent oxygen, with no cerebral vasoconstriction, you would end up with about a 200-mm venous carbon dioxide. With cerebral vasoconstriction, which does happen, you end up with about 75, and with carbon dioxide double in the cerebral blood flow, you have about 1000 mm on the venous side.

DR. PAPPENHEIMER: My comment started out to be the same as Dr. Rahn's, but with the addition that if you experimentally add carbon dioxide as you did, do you find as in that situation 100 per cent saturation in venous blood?

DR. LAMBERTSEN: Yes.

Dr. PAPPENHEIMER: Under those conditions then you should see a very large rise in the tissue carbon dioxide, and this would be a very simple experimental approach to the problem.

DR. LAMBERTSEN: In other words, you should see a sustained rise as shown in Figure 2.5-6.

DR. PAPPENHEIMER: That is right.

DR. STEIN: To answer another part of your question, Dr. Rahn, whether or not this could be an artifact; no, because the electrodes were immediately upon termination of the experiment placed in control solutions, and they showed the same responsiveness to the oxygen concentrations that we would expect. So I do not believe that the fall is an artifact. But how to explain its lack of persistence is beyond me.

DR. BEHNKE: Has anyone repeated the experiment?

DR. LAMBERTSEN: It has been done twice, has it not, by two different groups?

DR. STEIN: Yes, Davies and Brink, and Stein and Sonnenschein.

DR. BEHNKE: Is anyone able to measure gas tension in brain tissue directly? This thing was looked upon as an artifact at the time, and it would be

amazing if there had never been a check made of it.

DR. LAMBERTSEN: I think Dr. Behnke was at Bethesda at the time Gersh carried out the experiments there, and I believe Dr. Stein's were carried out in Chicago independently. You tended to check each other. The only thing that ever bothered me was that I could never understand the results. In the light of what seems to be a very much different pO_2, wherever you happen to be along the brain tissue capillary, you can almost pick out the pO_2 you want, if you can hit the right place.

DR. SCHMIDT: I would like to raise the question here as to how far one could go in transposing these results from animal experiments. Were they under anesthesia?

DR. STEIN: These experiments were not under anesthesia. They were curare experiments, and the animals were artifically respired.

DR. SCHMIDT: That takes away quite a good bit of my objection. Perhaps it is well known by all here that the intrinsic regulation of the human cerebral circulation presumably is a much more delicately poised thing and much more efficient than that of the experimental animals and that under anesthesia, even in man, the regulation is upset.

DR. STEIN: That bothered us, and we tried to get out of the dilemma by using curare.

DR. WENDELL: I would like to ask a question of Dr. Haugaard. As far as I know there are also enzymes, the activity of which is enhanced by oxygen. Has anyone ever thought of the possibility that oxygen might exaggerate the activity of an enzyme and thus exert the toxic effect? For example, amino oxidase activity is much higher in an atmosphere of 100 per cent oxygen than at 20 per cent.

DR. HAUGAARD: We did not study that enzyme. I do not think anyone has looked at it from that point of view.

DR. LAMBERTSEN: Your point is that most everyone has been looking for a depression of the enzyme system by oxygen.

DR. WENDELL: But there are enzymes which are more active at oxygen tensions higher than normal, and my question is whether abnormally high enzyme activity due to high oxygen pressure might be the cause of oxygen toxicity.

DR. BEHNKE: All this work concerning the high oxygen, partial pressure effects on enzymes is very essential. But what about the simple experiments of measuring oxygen consumption and carbon dioxide output in individuals at high pressure? Do you find any gross change in oxygen consumption or carbon dioxide output?

DR. LAMBERTSEN: I thought you had done it some fifteen years ago at the Experimental Diving Unit. As I remember, you found that up to 3 atmospheres

there was no difference in oxygen consumption. You did not measure carbon dioxide production. Is not that the case?

DR. BEHNKE: Yes.

DR. LAMBERTSEN: You used the basal metabolism apparatus technique and found oxygen consumption after the initial rise, which might be related to solubility of oxygen in tissue, was stabilized at about the same level of oxygen consumption as at sea level.

What we have done has been not to measure whole body oxygen consumption, but to measure the oxygen consumption of the brain by using the nitrous oxide cerebral blood flow technique of Schmidt and Kety and the arteriovenous oxygen differences. We found that while breathing oxygen at 3-1/2 atmospheres during rest, there is no change in either the oxygen consumption (per 100 grams of tissue) or in the carbon dioxide production of the brain. During exercise we get some strange situations where the oxygen consumption of the brain tends to be diminished by increased oxygen tension.

We do not understand it yet and would rather not mention it, but if we can at least say that ignoring bone, skin, and hair, and taking only the organ we are concerned with, the brain, oxygen at high pressure does not seem to change the rate of utilization.

Referring again to Figure 2.5-6 it is quite evident that somewhere along the capillary there is going to be a rather tremendous mass of brain tissue not exposed to high oxygen tension, so that we might be completely unable to measure a change in oxygen consumption of the few brain cells that might be very badly poisoned by oxygen. We might not be able to measure the thing for which we are looking.

DR. BEAN: In this connection I believe the experiments of Dr. Elizabeth Cass are very important. She probably used pressures a little higher than these, but just how much I am not sure. In muscle, and in nerve particularly, she found an initial increase in carbon dioxide production which was very marked -- as much as 50 per cent -- then a very marked drop. This was in isolated tissue. It seems to me these experiments are particularly significant, not only in view of the fact of the reduction of oxygen metabolism as indicated by oxygen consumption and by the carbon dioxide, but also because of the finding that there was an initial increase in carbon dioxide, which brings us back again to a consideration of carbon dioxide as probably a very important initial contributory factor. These were not circulated tissues, but it would seem the findings are rather significant in this situation also and so are related to Dr. Behnke's question.

DR. STEIN: Since Dr. Behnke and Dr. Bean are both baiting me, I guess I will have to rise to it. We did do several experiments in which we measured total carbon dioxide output and oxygen consumption in the whole organism. But unfortunately, we did not trust our carbon dioxide analysis. The analyzer used was a far cry from that we have available to us today. We are preparing to set up in our own laboratory the experiment Dr. Behnke mentions. I do not recall we spoke of fifteen years, but I will admit to ten, during which we have been

fussing with this thing, mostly from a technical point of view.

The present infrared type analyzer seemed to be the answer to the difficulty, at least in setting up the experiment. Perhaps at our next meeting, Dr. Behnke, we can give you an answer to this.

DR. LAMBERTSEN: We actually measured the carbon dioxide production in a group of men and found it was increased at rest at 3-1/2 atmospheres and not decreased as you might expect if carbon dioxide were to be accumulating in the tissue. So we haven't measured simultaneously the oxygen consumption and carbon dioxide production,but have measured the carbon dioxide production of the whole body oxygen consumption of the brain. That might help some.

DR. BURTON: I would just like to ask a question before I worry about the spike in the polaragraph records. The fall coincides with the convulsions. Can anybody tell us what happens to the blood flow of the brain during those convulsions?

DR. LAMBERTSEN: Can I refer you to Dr. Schmidt who has been worrying about this for a long, long time?

DR. SCHMIDT: I can tell you about the rhesus monkey under light anesthesia. At the moment of a metrazol convulsion the blood flow goes up about 60 per cent and the cerebral oxygen uptake is approximately doubled. What happens in man, I do not know. We have been playing around with it, but the nearest approach we can get with Kety's methods is just before or just after the convulsion. Just after the convulsion the cerebral blood flow of man is subnormal, coinciding with a metabolic acidosis and a respiratory alkalosis, probably related to the muscular activity of the convulsions. What happens at the instant of convulsion in man, I do not know. I have been trying to talk my anesthesiological colleagues into doing the experiment, but not successfully.

DR. REYNOLDS: I wonder whether Dr. Stein made any estimates of the actual volume of oxygen that has to be done away with in unit time?

DR. STEIN: No, we have not, Dr. Reynolds. I do not know the answer.

DR. REYNOLDS: I just think it should be possible to compute the approximate amount of oxygen that would be used by the volume of tissue involved, and from that to find out whether the rapid decrease in oxygen tension observed is explainable by the metabolism of the brain tissue.

DR. BEAN: How long was this peak continued?

DR. STEIN: The peak was rather short. It varied as it will in individual animals, but it seldom persisted more than a few minutes, then the potential dropped and did not rise again.

DR. BEAN: On general principles, sound physiologics, it almost makes one think of artifacts here.

DR. STEIN: Yes, I wouldn't want to stand on this. I merely report it as we see it. There is certainly a great deal of question in our minds as to how to interpret it if it is not an artifact, and I will accept it as being an artifact until proven otherwise.

DR. LAMBERTSEN: Dr. Burton, you raised the question of blood flow during convulsions. As Dr. Schmidt pointed out, the only information available is in the monkey. However, during the oxygen convulsion there is a very severe breath-holding period about one minute and a half to two minutes, during which there is violent muscular activity. If the carbon dioxide tension of arterial blood affects cerebral blood flow, it would be interesting to see what the effect in the initial period of the convulsion was upon cerebral blood flow and the brain tissue carbon dioxide. There should be a spike in alveolar carbon dioxide and possibly then a short spike in cerebral blood flow, perhaps tying some of these discordances together.

Could I ask Dr. Penrod to tell us a little bit about the effects of nitrogen or inert gases on oxygen toxicity?

DR. PENROD: That is quite a sizable subject, of course, but I think you have summarized it best of all when you said that in some manner the intermittency with nitrogen of oxygen exposure seems to prolong greatly the period of freedom from symptoms which result in high pressure oxygen. We, too, have had results much like those that you have already given us here, that is, if you intermittently expose to relatively small nitrogen concentrations, you can prolong the duration of oxygen exposure very greatly. We have tried a number of different nitrogen combinations. We have attempted to re-evaluate that old question of whether a nominal amount of nitrogen approximating that normally found at 1 atmosphere has any physiological effect and is necessary. We have exposed animals at 4 atmospheres total pressure to a partial pressure of nitrogen of 680 mm, the balance being oxygen; that is, 4 atmospheres less 680 mm, and we find it has no effect whatsoever on their survival. Therefore, I think that nitrogen can still be considered to be perfectly inert, physiologically, in any quantity of which we know.

It is still entirely conceivable that nitrogen can be playing a subtle part other than simply reducing the partial pressure of oxygen when it is mixed in with these gases, and as Dr. Lambertsen had proposed some time ago, perhaps in some way it could be having a physiological effect that might mask some of the manifestations of oxygen toxicity. So far we have found no evidence in that direction. After a fair amount of experimentation with nitrogen, I can add nothing further to our present knowledge of the role of nitrogen in oxygen toxicity.

DR. LAMBERTSEN: Have you considered nitrogen at very high pressures?

DR. PENROD: No, I have not done any nitrogen exposures at levels in excess of 4 atmospheres.

DR. LAMBERTSEN: At narcotic levels?

DR. PENROD: No, I have not gone into the narcotic levels. Four atmospheres is the highest I have gone with mixtures of oxygen and nitrogen.

DR. LAMBERTSEN: And the highest nitrogen pressure itself, would that be about the same as here?

DR. PENROD: Yes, I have used air at 4 atmospheres, and I have not had any apparent narcosis of nitrogen effects.

DR. OWEN: I would like to ask Dr. Haugaard if he can give us anything about the relative rates of oxidation and subsequent reduction of the sulfhydryl enzymes. It seems that if the intermittent high oxygen guinea pig experiments are valid, the rate of recovery is approximately twice the rate of development of the toxic process under these conditions. This would imply that reduction of the enzymes conceived in a low-oxygen environment proceeded more rapidly than their oxidation under high oxygen.

I wondered if that concept integrates with the sulfhydryl idea.

DR. HAUGAARD: To this I can say that the oxidation of glutathione, at least, and probably some of the other coenzymes, is a slow process, but there are enzymatic mechanisms by which these sulfhydryl coenzymes can be reduced.

If you take glutathione, it is known that hydrogen from triphosphopyridine nucleotide can be transferred to oxidized glutathione to reform the reduced substance.

So there are mechanisms by which glutathione could be reduced at a rate quicker than we would expect it to be oxidized by oxygen.

DR. YARBROUGH: I am sure the discussion indicates we are all interested in the mechanism of the oxygen toxicity. I have, however, heard no discussion this morning of the variable characteristics of oxygen toxicity susceptibility. This is certainly one of the most impressive phases of the phenomenon, particularly in humans. One day a man has apparently unlimited tolerance to oxygen under pressure, and the next day he gets a paroxysm in five minutes.

I wonder, in seeking the mechanism, should we not explore this road of the explanation of why the variability? Perhaps that is going to give us an answer. Does anyone here have any explanation of the variability?

DR. LAMBERTSEN: We are not at all sure why major stresses, like carbon dioxide stimulation and exercise, shorten the latent period. It is very hard to come up with a good explanation of why a man sitting here minding his own business should change from one day to the next. I certainly agree that if we find the explanation of variability, we will have a great deal of information.

DR. YARBROUGH: Is it true that you don't see the variation in the animals as you do in the human?

DR. BEAN: I agree with you and I feel very emphatically that this is one of the very important and striking characteristics of oxygen toxicity in animals as well as humans and I just wonder whether it might represent the subtlety of a number of factors operating together, and if you get them all operating together in the right direction at the right moment, they click. If you do not, you may have something else. That is just speculation, of course.

DR. LAMBERTSEN: Could I ask Dr. Bean to speculate on just one more thing while we have him here, that is, the species difference.

He has shown us some beautiful slides of the pulmonary damage in small animals exposed to oxygen at high pressures, and to my knowledge we have not as yet had a true case of pulmonary damage in humans in the many thousands of people who have now used oxygen at high pressure. Have you an explanation for species difference that we find in pulmonary damage by oxygen?

DR. BEAN: No, I have not. There are some differences in age. I think that Hyman, Drinker, and their group found very young animals to be more resistant as far as pulmonary damage was concerned, but I am not agreed that there is not some damage in all forms, including man, under certain proper conditions. I think it is easier to produce them in some forms than others, but what the species difference would be, I do not know. I do not doubt that there is damage in humans as well.

DR. LAMBERTSEN: You mean you could have pulmonary damage if you exposed them long enough?

DR. BEAN: Yes, and even in those exposures that are not very prolonged, I am sure there may be subclinical effects. What I am interested in is not so much from the pulmonary side, but it represents to me a more or less general effect, probably on the vasculatory system.

DR. PENROD: This pulmonary effect got in my way for so long when I was looking for other things that I finally gave up and started doing some work in that direction and made the fundamental mistake of not first thoroughly consulting our pathologists. I made a good series of observations and was a bit disturbed over the fact that my controls also did not look as good as they might. When I called in my pathologist colleagues, they informed me there is existent, particularly in rats and other small laboratory animals, an endemic pneumonic type condition which is simply exacerbated by the oxygen toxicity. They proceeded to show me a great many things in the control slides that were apparently predisposing to conditions in the experimental ones and convinced me that this situation exists in probably all rat colonies, and that to a certain extent what we were finding on smaller animals, extending into guinea pigs and rabbits, was a pandemic condition that was perhaps only exacerbated by the oxygen and therefore was not representative of what you might expect in healthy adults. I am merely quoting someone else on this. This is not my own opinion.

DR. STEIN: If I may add to this subject, the same difficulty besets all of us entering this field, and we too found we had a great deal of pulmonary damage from both monkeys and cats. But when the question of anesthesia, as Dr. Schmidt

brought up, entered our minds, we went to the curare experiments. In order not to overdistend or underdistend the lungs of our animals, we determined the tidal volumes of our animals before placing them on the artificial respiratory device or pump. When that was done, we found that the lung damage we had seen in animals placed in a chamber and permitted to breathe on their own disappeared, and subsequent to that we didn't have the pulmonary involvement that has been described so many times.

Now to take the data of others and to evaluate it along with those which you yourself get, is a bit difficult for me to do. I don't know how to evaluate them because all the conditions of the experiment are not known. We believe that a majority of the lung damage seen in animals exposed to high pressures of gases, particularly oxygen, is mechanical, and that if provisions are made not to overdistend the lungs, you do not get a great deal of damage. This has been done many, many times.

DR. PENROD: Before we close I should like to say one more thing. I don't understand why this discussion has proceeded as far as it has this morning with no reference being made to this newer concept, which Dr. Gershman has published recently, of the relation of radiation damage to oxygen toxicity. I am not prepared to discuss it myself at all, but certainly the data that have been presented recently on the similarity of reactions to radiation damage and to oxygen toxicity are striking as far as I am concerned, and I hoped to hear somebody discuss that a good deal more.

I have personally felt for some time that there was good likelihood of some relationship between oxygen and ozone toxicity. The pathology described for ozone toxicity is very similar, and many of the other reactions are quite similar. This seems to be a whole facet of oxygen toxicity that hasn't been mentioned this morning. I wonder if anyone could elaborate on that.

DR. LAMBERTSEN: No, not better than you have already.

DR. BEAN: I might say Ozorio de Almeida in Brazil in about 1940 was carrying out experiments on humans. I never saw anything published about it. At the time I was down there, they were working on combining X-ray and oxygen in high pressure in treatment of carcinomatous conditions.

I should like to bring up one more question, Dr. Lambertsen, and that is in the picture you showed in your paper a while ago regarding the change in the venous acidity as you went from the normal to the higher oxygen pressures, there was a progressive decrease in pH, which to me was a significant thing, because years ago we found that in dogs exposed to oxygen at about 3 atmospheres and a little above, the venous blood did take such a change as you have shown. I wonder whether, again, it might not be acting on some central mechanism.

3.1 OUTLINE OF PROBLEMS OF DECOMPRESSION AND BENDS

A. R. Behnke
Captain, Medical Corps, USN
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The major problem is the perennial one of administration, not investigation, and revolves around personnel. Costly pressure chamber installations, even replete with airconditioning, which make possible tests at simulated depths of 1000-feet, "push button" gas analyzers, ample funds, and three new tools, 1) radioisotopes, 2) in vivo methods of determining body fat, total body and extracellular water, blood volume, and 3) availability of sizable quantities of inert gases, all should have served to make this past decade, following the experience gained during World War II, a "golden one" not only in applied problems, but in basic, although piecemeal, physiological and biochemical studies which form the usual university research endeavors.

With reference to personnel it is necessary to eliminate the 40-hour week, civil service investigator since experiments in compressed air do not lend themselves to the 8-hour day. With reference to personnel in uniform there is only one Navy physiologist devoting full time to underwater swimming problems. With reference to naval support of the thousands of American youth interested in underwater swimming, who could well be directed by Naval Reserve, as well as active personnel, in the interest of providing pre-naval training and preventing disability and injury, it has been singularly lacking.

We look to civilian physiologists, therefore, to extend the postwar efforts of Fenn, Lambertsen, Gerschman, Carpenter, and Bean. Particular effort is required to elucidate mechanisms with the new tools at hand rather than confirm the descriptive phenomena of the older physiologists. Some topics that appear amenable to accelerated research are set forth as follows:

HIGH OXYGEN PRESSURES -- RESPIRATION

Effect of high oxygen pressure on respiration.
  Nature of convulsive respiration and the paralysis of respiration by oxygen.
Neuromuscular pathways involved in the diaphragmatic spasm.
Nature of the altered response to carbon dioxide following oxygen inhalation.
Is the irritant effect of oxygen on the respiratory tract and pulmonary edema a direct effect of oxygen or secondary to pituitary-adrenal hormone responses?
Measurement of oxygen consumption and carbon dioxide elimination in the intact animal subjected to high oxygen atmospheres.
Adaptation to high oxygen pressure.
Will prolonged residence in an atmosphere of 60 per cent oxygen permit increased tolerance to high oxygen concentrations?
Does altitude residence decrease tolerance to increased oxygen?
What is the effect of prolonged residence in an atmosphere rich in oxygen

but devoid of toxicity (0.6 atmosphere), e.g., on hematopoiesis?
Detailed mechanism underlying tubular vision induced in man at 3 atmospheres pressure.
Basis for the symptom of nausea.
Is oxygen a radiomimetic agent?

NATURE OF BENDS

Can the blood stream hold gas in a state of supersaturation?
When do silent bubbles become clamorous ?
Demonstration of the bubble state on the basis of altered nitrogen elimination from the body.
What is the course of nitrogen elimination following injection of known quantities of gas in bubble form?
Preponderance of evidence favors intravascular bubbles as cause of bends. e.g., long exposure in compressed air is not necessary to produce bends.
Bends occurs following short exposure to high air or helium-oxygen atmospheres.
Does helium with its high diffusion rate and low lipid solubility form extravascular gas bubbles?
Mechanism of tachypnea and the deep inspiratory test pathognomonic of pulmonary embolism.
Gersch has demonstrated the distortion of pulmonary vessels filled with bubbles. What reflexes are initiated by distension of pulmonary vessels during deep inspiration?
To what extent is the Hering-Breuer reflex involved?
What do single nerve fiber techniques reveal?
Bubble formation under conditions of hypothermia.
Effect of bubbles on circulation.
Further application of cinematographic and microhistologic techniques.
What is the modus operandi of heart muscle function under the extreme hypoxia induced by bubble emboli?
Mechanism of shock.

BIOCHEMICAL STUDIES

Nature of malaise following rapid decompression.
Is malaise due to slowed circulation or to an adrenal depression related to the presence of bubbles in the adrenal cortex as demonstrated by Gersch?

PATHOLOGICAL

Production of the bone lesions seen in caisson workers and in lower animals.

MATHEMATICAL -- PHYSICAL

A generalization is required to guide decompression of divers. Haldane's rule (the 2 to 1 ratio) is not satisfactory for decompression from exceptionally deep depths or following prolonged (saturation) exposures in

compressed air. Decompression utilizing a relative pressure difference, ΔP, e.g., of 18 pounds per square inch, unduly prolongs decompression. The formulation should include a factor relating to the pressure level (number of gas molecules) from which decompression takes place as well as factors of diffusibility, solubility, and viscosity of inert gases.

Saturation experiments at high pressures on animals should serve to check the validity of the calculations.

A TEST FOR ADEQUATE DECOMPRESSION

The innumerable tests of aviators in low-pressure chambers, although uncontrolled for the most part with respect to the many physical and physiologic variables involved, tend nevertheless to show that decompression from 1 to 1/3 atmosphere, i.e., from ground level to an altitude of about 27,000 feet, does not give rise to bends in the resting individual.

Following decompression of divers, the low-pressure chamber could serve as a rapid means of determining the completeness of elimination of excess nitrogen and the role of the "slow tissues" in bringing about bends.

3.2 BUBBLE FORMATION

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Biology Department
Princeton University

INTRODUCTION

The type of bubble I first propose to talk about is the one that forms under as simple conditions as possible, in water, in contact with various surfaces as a result of pressure differences in the liquid, a quantity whose meaning will be evident in a moment. Then we shall consider the bubbles that form in body fluids in contact with cells and tissues.

FORMATION AND STABILITY

There are two problems involved in bubble formation. The first is how the bubble starts and the second how it grows. I think that in most cases we can say a bubble starts from some preformed gas phase, from what can be called a gas nucleus. When I use the word 'nucleus', I use it in a different sense from a chemist who talks about a nucleus for crystallization, because the bubble nucleus is always a gas or vapor phase rather than a solid particle. It may be a very stable gas phase, particularly if the nucleus is on a surface which is hydrophobic.

A small spherical gas bubble in the center of a liquid will eventually disappear, simply because the internal gas pressure due to surface tension in the bubble is sufficient to force the gas into solution. In magnitude the internal pressure due to surface tension is twice the surface tension divided by the radius of the bubble, so that if a small bubble is to be stable, it is necessary to increase the gas pressure in the liquid -- or let me call it gas tension in the liquid -- in order that the bubble may not disappear.

On the other hand, if a gas mass sticks to a hydrophobic surface, the curvature may be very slight, and such nuclei can last indefinitely. If there is a crack present with a sharp angle, any gas which fills the crack may actually be under a negative pressure because the gas-liquid surface is concave and may even continue to grow, although the liquid and the gas dissolved in the liquid are at atmospheric pressure. The gas nucleus is thus the starting point of most bubbles.

Figure 3.2-1C will illustrate the type of bubble which forms underneath a glass surface which is wet by water. It is practically a sphere, and the gas phase does not really contact the surface. But if the surface is paraffin, as shown in B or D and E of Figure 3.2-1, then the gas actually clings to the surface, and there is a large contact angle between the gas and the surface itself. It is under these conditions that one can obtain bubbles which are very, very stable and very hard to remove.

GAS TENSION

When soda water is poured into a glass tumbler, the bubbles that form are

all due to gas nuclei. Let us suppose we completely free a liquid from any of these minute nuclei. The question then arises whether bubbles can form. It has been found that very great differences in pressure, Δ P, are necessary to form bubbles under these circumstances. By differences in pressure I mean the difference between the gas tension in the liquid, p, and the actual hydrostatic pressure, P, which is often referred to as $\Delta P = p-P$. It is the fundamental driving force for bubble formation. The ΔP may be made large, either by greatly supersaturating the water with gas, or by actually subjecting the water or other liquid to a negative pressure.

Theoretically, bubbles should form under these conditions only if the pressure difference is of the order of 100 to 1000 atmospheres. These are pressure differences that are never found in altitude or in diving experiments. In the laboratory they can be attained. Water can be saturated with gas at 100 atmospheres pressure, and then if allowed to stand undisturbed and the system is free of gas nuclei, no bubbles will form.

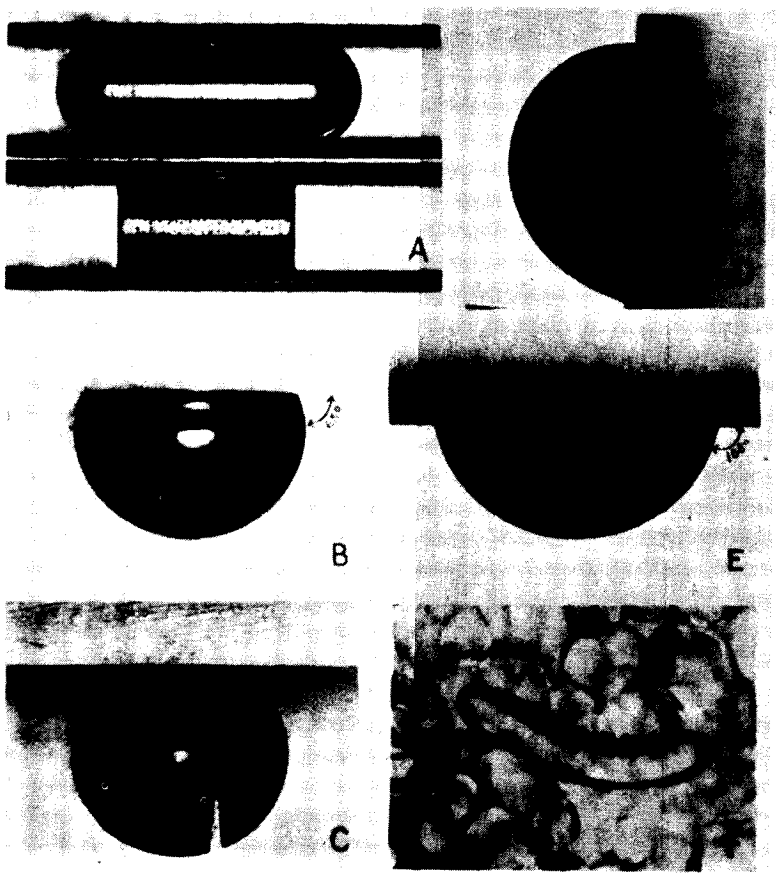


Figure 3.2-1 Shapes of Bubbles under Various Conditions

It is also true that one can take water, which has no gas nuclei in it, exert a pull on a water column, subject it to very high negative pressures, as much as 200 atmospheres, and there will be no bubbles formed in the liquid. Perhaps I should say there will be no cavities formed in the liquid because when water is pulled apart, a cavity is formed first and if any dissolved gas is present, the gas molecules immediately jump into the cavity and form a tiny bubble that can remain as a gas nucleus when the negative pressure is removed.

BUBBLE FORMATION IN TISSUES

The first question that might be asked in connection with animals is whether there are any gas nuclei normally present in their blood, between the cells or actually within the cells. If the blood vessel walls were hydrophobic, there would be every reason to look for gas nuclei. The nature of the wall can be tested by noting the shape of a gas mass in a small blood vessel. In the 'A' section of Figure 3.2-1 there is a bubble in a glass tube filled with water (above) and in a paraffin tube filled with water (below). In the upper figure the air bubble has rounded ends. In the lower part of 'A' the bubble ends are actually concave, although one cannot see the concavity because of light reflection effects. The 'F' section of Figure 3.2-1 contains a photograph of an air bubble in a vessel in fatty tissue of the rat. It will be noted that the ends are rounded, demonstrating a hydrophilic vessel endothelium, or one which is on the average hydrophilic. Such walls should not hold gas nuclei.

During the war a group of workers associated with me at Princeton University carried out experiments on cats in which blood was withdrawn from the aorta into very clean tubes, free of adhering gas nuclei, and then subjected to the vapor pressure of the blood itself. Under these conditions of reduced pressure the blood never formed bubbles, provided the experiment had been done properly to remove gas nuclei. Therefore it does not look as though there were any gas nuclei present in the blood.

A similar experiment can be carried out with tissues which are carefully taken from the body to avoid contamination with gas nuclei and subjected to a high vacuum. Bubbles do not form. On the other hand, if a high gas pressure experiment is carried out with rat tissues removed under conditions where no gas nuclei can be introduced and then saturated with gas at, let us say, 10 atmospheres pressure, it is found that on sudden decompression an occasional bubble may form, but usually there are none. If 80 atmospheres gas pressure of nitrogen is used, these tissues will usually form bubbles. It looked as if under these circumstances with rather high ΔP, there were either minute gas nuclei present, or some other condition in the system which favored bubble formation.

The one other condition that regularly results in bubble formation is to have the liquid in motion or to manipulate the surfaces in the liquid. It can be demonstrated with tissues supersaturated with gas and then decompressed that a slight movement or manipulation of the tissue with a microneedle will result in bubble formation, whereas under the same conditions at rest, no bubbles appear.

EFFECTS OF MOTION

Returning now to the simple condition of water in a vessel, it is extremely difficult to obtain either bubbles or cavities, no matter how much the liquid is supersaturated with gas or how great a negative tension is applied. However, if the liquid is put in motion, especially in contact with surfaces, bubbles will form, I think, because of local, negative pressure regions set up within the liquid. This is particularly true wherever a liquid comes in contact with a surface because then the liquid can be pulled away from that surface fairly easily, leaving a small cavity behind.

There are various methods by which one can obtain local tensions in a liquid in motion. If the liquid as a whole is in motion, local low-pressure regions result as it flows through a constriction in a pipe, as in the well-known Reynolds' cavitation, when a stream of bubbles will form. Figure 3.2-2 shows a glass tube in which water is flowing upward through a constriction. The small white regions just above the constriction are masses of bubbles which form as a result of the low pressure in the narrow part.

It is easy to demonstrate this effect in the laboratory by attaching a rubber tube to the faucet and with water flowing through it, pinch the tube until the lumen is considerably decreased, when one can feel the bubbles that form as a result of the constriction. I have often wondered if in the flow of blood through arteries in the body, bubbles could form from the squeezing of arteries by muscle contraction.

Second, wherever a vortex forms, as in turbulence, one can have fairly large negative pressures at the center of the vortex. Third, if a surface is moved rapidly in water, the water cannot always follow the surface. There will be left behind a cavity, and bubbles will frequently form as a result of these sudden movements of surfaces. This effect can be demonstrated by hitting a glass

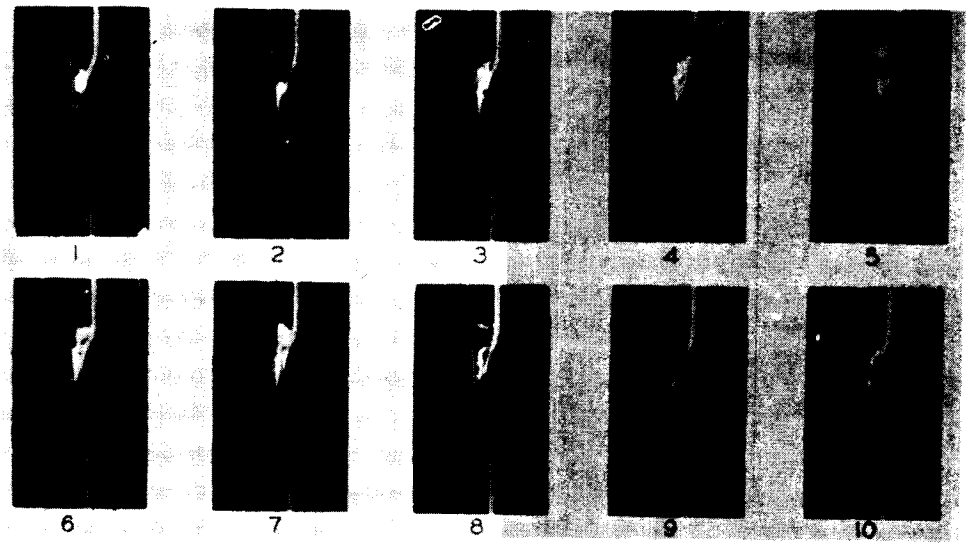


Figure 3.2-2 Reynolds' Cavitation

tube containing water which has been slightly evacuated. For quantitative control the blow can be delivered by a wooden block attached to a bar of iron whose movement is actuated electromagnetically. Every time the tube is hit, the glass is moved slightly, and cavities will appear at the glass surface. They then collapse to small bubbles which rise in the tube. Figure 3.2-3 is a series of prints from a moving picture by which the duration of the cavities can be measured.

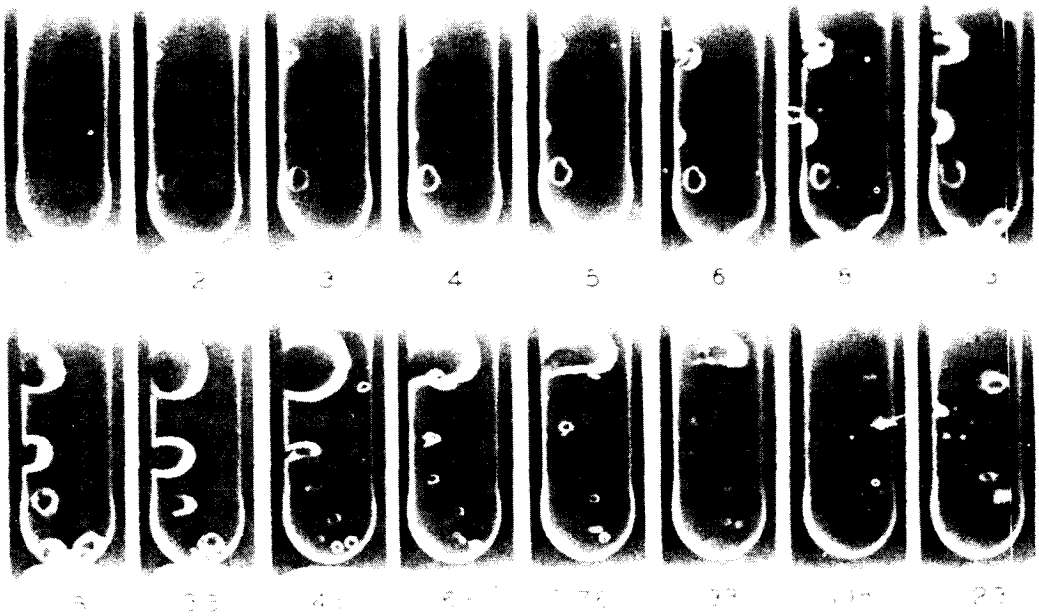


Figure 3.2-3 Bubble Formation Resulting from Cavitation

Another method of forming cavities at a moving surface is illustrated in Figure 3.2-4, showing the end of a rod moved rapidly through corn syrup of very high viscosity. Under these conditions what happens to the cavity becomes much more apparent since it cannot disappear as readily as in a non-viscous medium like water. The large cavity remains for some time. In water the cavity oscillates several times before disappearing. Gas molecules can easily diffuse into such a cavity and remain as bubbles on collapse.

One can see immediately what would happen if we were dealing not merely with a viscous substance like corn syrup, but with a material which was actually a gel-like tissue -- any slight movement would pull that gel away from a surface and result in a minute cavity. Once the minute cavity was formed, any gas dissolved in the gel would immediately move into it and form a gas space.

Finally, it is possible to obtain local changes in pressure, both positive and negative, whenever pressure pulses pass through the water. Such pressure fields result whenever shock or sound waves, which are made up of a positive-followed by a negative-pressure region, move through a liquid. When a positive pressure shock wave is reflected, it becomes a negative wave.

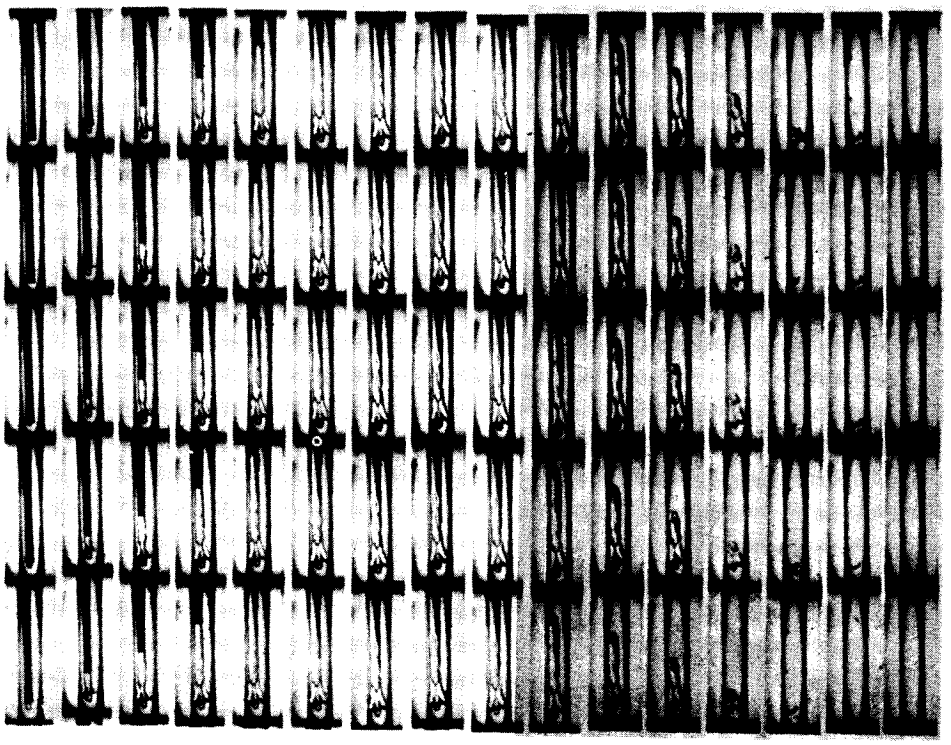


Figure 3.2-4 High Speed Photographs of Cavitation

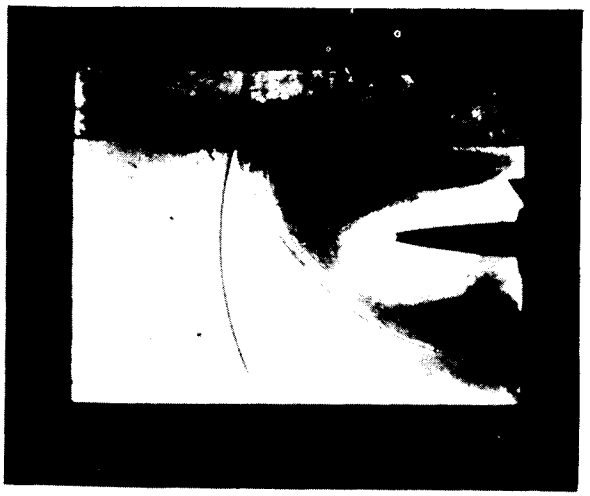


Figure 3.2-5 Shock Waves in Water

Figure 3.2-5 shows the bubbles that form as a result of a pressure pulse, a shock wave, which has come from a bullet fired into a water tank from the side. The black triangular spike to the right is the cavity behind the bullet. The initial shock wave resulting from first contact with the water is at the left. As this wave is reflected from the surface of the water, the second shock wave at an angle is really a negative pressure wave, which has caused a mass of black bubbles to appear in the water behind it. If a shock wave should pass through tissue, a similar bubble formation might occur.

It is thus apparent that any cavity formation in a liquid is immediately followed by bubble formation on collapse of the cavity, and our next problem has to do with the growth of these minute bubbles. Growth will occur whenever ΔP is positive, but even more important for growth is the kind of gas which is present. When gas molecules diffuse into cavities, the rate of diffusion is chiefly dependent on the number of molecules of gas in the liquid, that is, upon the solubility of the gas. If one gas is fifty times more soluble in water than another gas at a given pressure, the more soluble gas will enter the cavity fifty times more rapidly. Therefore carbon dioxide becomes of great importance in bubble formation.

If you wish to convince yourself of that fact, you can set up the following experiment. Take a long tube which can be connected to a vacuum pump and first fill it about one third with water saturated with air. Then add a layer of water saturated with carbon dioxide. Finally, place above that another layer of water saturated with air. The tube should then be evacuated slightly so that it is under reduced pressure.

Now if the bottom of this long tube is struck a blow, minute bubbles will be formed, little gas nuclei which will rise through the liquid relatively slowly because they are small. When they enter the carbon dioxide saturated region, they suddenly increase in size at a rate that can be seen readily. They now move up through this carbon dioxide layer very rapidly. When they come into the air-saturated region again, they shrink, and their rate of rise again becomes much slower. Remember that these gases are all saturated at 1 atmosphere in their respective water layers, but because of the difference in solubility, the bubbles in a carbon dioxide region grow very rapidly. I think this is a very striking demonstration of the effects of different gases on the growth of bubbles.

Now during the war we experimented with cats at simulated high altitudes, observing bubbles that might form in the animal by watching the posterior vena cava. The animals were opened under Nembutal anesthesia, placed in an altitude chamber, and then observed under low pressure. We found that bubbles would rarely form in these cats at 45,000-foot altitude if they remained motionless, but if the muscles of the hind legs were stimulated, bubbles formed very readily and could almost always be seen moving in the vena cava. I would say, therefore, that in the body, muscle contraction is the most important factor in bubble formation, and that it introduces the conditions of a fluid in motion, with all the physical factors favoring bubble formation about which I have been speaking.

Here is another most interesting and significant thing. It is not merely during decompression that muscle contraction will facilitate bubble formation. If one stimulates the muscles of the hind legs of anesthetized cats to contract before the cats are exposed to high altitudes (prestimulation), then bubbles will form at altitude even though they are completely at rest. This effect of prestimulation takes considerable time to wear off.

SUMMARY

So far as practical applications go, I would say that our experiments indicate that a person should be kept as quiet as possible, not only after decompression, but should also be kept quiet for a little time before he is decompressed.

Muscular exercise evidently starts the formation of gas nuclei, which on decompression may grow to a considerable size.

The other point is, of course, that during the period of compression a person should breathe non-toxic gases which are least soluble in water so that the conditions will be least favorable for growth of bubbles after decompression. One should increase the circulation for rapid gas exchange, although it should not be increased by muscular exercise but by some other method. In short, one should avoid movement and avoid the accumulation of carbon dioxide.[62]

3.3 OXYGEN DECOMPRESSION

A. R. Behnke
Captain, Medical Corps, USN
U. S. Naval Radiological Defense Laboratory

I shall enumerate a series of topics which serve to invite attention pertinent to research, for the most part not annotated in the "Source Book of Compressed Air, Diving and Submarine Medicine", by Hoff and Greenbaum.[63]

THE FIRE HAZARD

Individuals have been burned to death in chambers in high oxygen atmospheres. The strictest safeguards must be enforced.

RATIONALE UNDERLYING THE EMPLOYMENT OF OXYGEN

Inhalation of oxygen promotes the elimination of inert gases from pulmonary capillaries into alveoli at a maximal pressure head. In diving operations this serves to shorten decompression or recompression (treatment) time from 30 to 50 per cent. In the surface decompression tests of Van der Aue, et al,[64] with oxygen inhalation taking place for the most part in a pressure chamber, decompression time for air dives was shortened about 45 per cent by the use of oxygen.

OPTIMAL CONDITIONS FOR THE INHALATION OF OXYGEN

The resting diver inhales oxygen from a closed system in a chamber at pressures corresponding to diving depths of 60 feet or less. This is accomplished in surface decompression (American procedures) and in the Davis (British) submersible chamber technique.

OPTIMAL STATE FOR INERT GAS ELIMINATION FROM THE BODY

Inert gas dissolved in the tissue of the body exists at a partial pressure equal to or less than the ambient pressure. This can be achieved by the inhalation of oxygen at atmospheric or higher pressures. The course of nitrogen elimination under these conditions is shown in the following graph, Figure 3.3-1.

CHARACTERISTIC OF THE NITROGEN ELIMINATION CURVE

Cumulative nitrogen elimination when oxygen is inhaled proceeds at a gradually diminishing rate, both absolute and relative. Thus, at atmospheric pressure (pH_2 573 mm Hg) about 50 cc of nitrogen per minute leave the body during the initial period of oxygen inhalation, and this is later reduced to less than 0.1 cc per minute after nine hours of oxygen inhalation. In terms of the relative rates of elimination, there is a gradual reduction from 1 (initial rate) to less than 0.1 (nine-hour rate). The experimental semilogarithmic (not a log log relationship) nitrogen-elimination curve can be broken down into five or more of its component semilogarithmic constant rate curves. This analysis reduces to quantitative form Haldane's concept of nitrogen elimination from some five tissues with respective half-saturation rates varying from 5 minutes or less to 75 minutes or more.

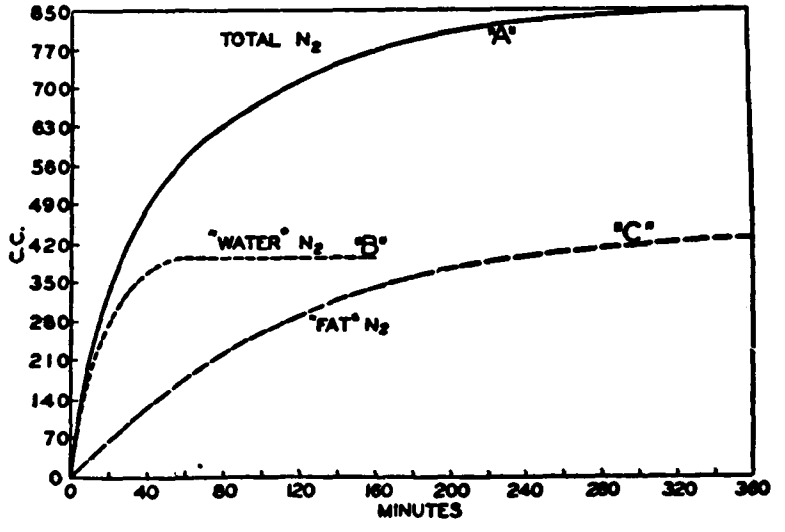


Figure 3.3-1 Nitrogen Elimination from Humans at Atmospheric Pressure while Breathing Oxygen (From Behnke, U. S. Nav. Med. Bull., 35:219, 1937)

I have chosen to represent the manner in which nitrogen is eliminated from its body solvents, the fluids and lipids. At the present time such an analysis becomes especially meaningful since body fat, blood, and total fluid volumes can be determined accurately in the living individual. This permits us to know the answer to the old imponderable -- the total nitrogen content of the body. The following curves were obtained on anesthetized dogs of different ages, sizes, and fat content (Figure 3.3-2).

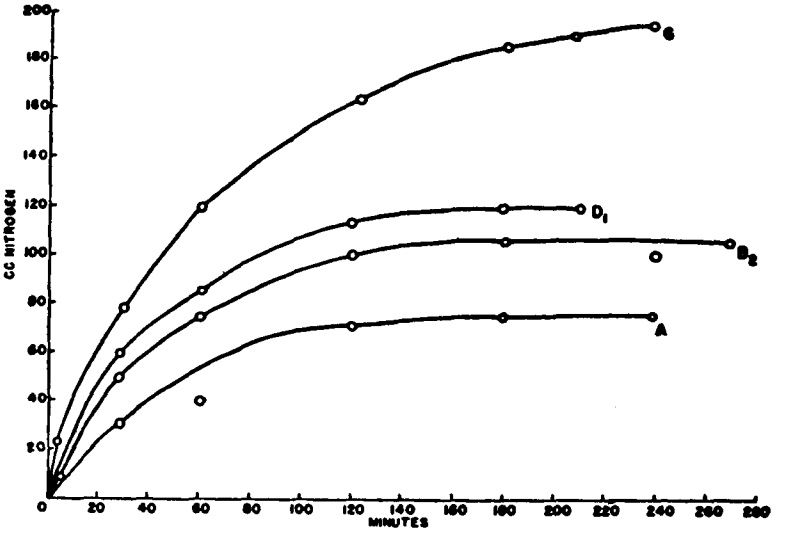


Figure 3.3-2 Nitrogen Elimination from Dogs at Atmospheric Pressure while Breathing Oxygen (From Shaw, et al, Am. J. Physiol., 112:545, 1935)

CUTANEOUS DIFFUSION OF GASES

An interesting phenomenon which has never been accorded the investigation it merits is the exchange of gases between skin and ambient air as demonstrated by the pioneer work on cutaneous respiration by Shaw, et al [65] and by studies of inert gas transfer. Thus nitrogen elimination will never be complete from the body under the conditions of oxygen inhalation previously described, since about 15 cc of nitrogen per hour diffuses percutaneously from ambient air. It has been shown that helium diffuses with sufficient rapidity through the skin to enable estimates of peripheral blood flow to be made, Figure 3.3-3. [66]

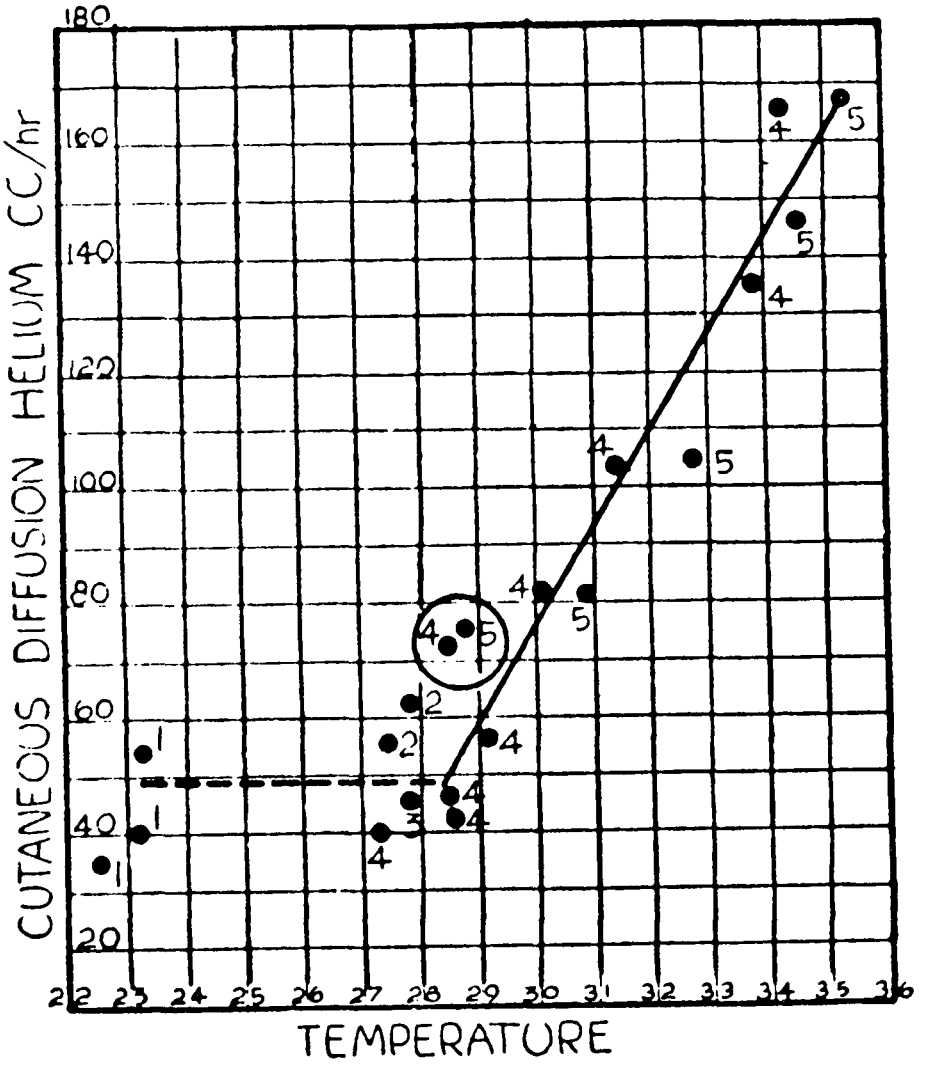


Figure 3.3-3 Cutaneous Diffusion of Helium in Relation to Temperature (From Behnke and Willmon, Am. J. Physiol., 131:627, 1941)

NITROGEN ELIMINATION FROM THE BODY UNDER CONDITIONS OF APPARENT SUPERSATURATION

The same anesthetized dog was exposed on different days to oxygen inhalation in a closed system at atmospheric pressure following previous nitrogen equilibration at 1, 3, and 4 atmospheres. From Figure 3.3-4 it is difficult to conceive of anything other than a 'state of supersaturation' existing during and subsequent to rapid decompression, for example, from 4 to 1 atmospheres. There is no 'break' in or distortion of the normal nitrogen elimination curve to indicate the presence of the "bubble state".

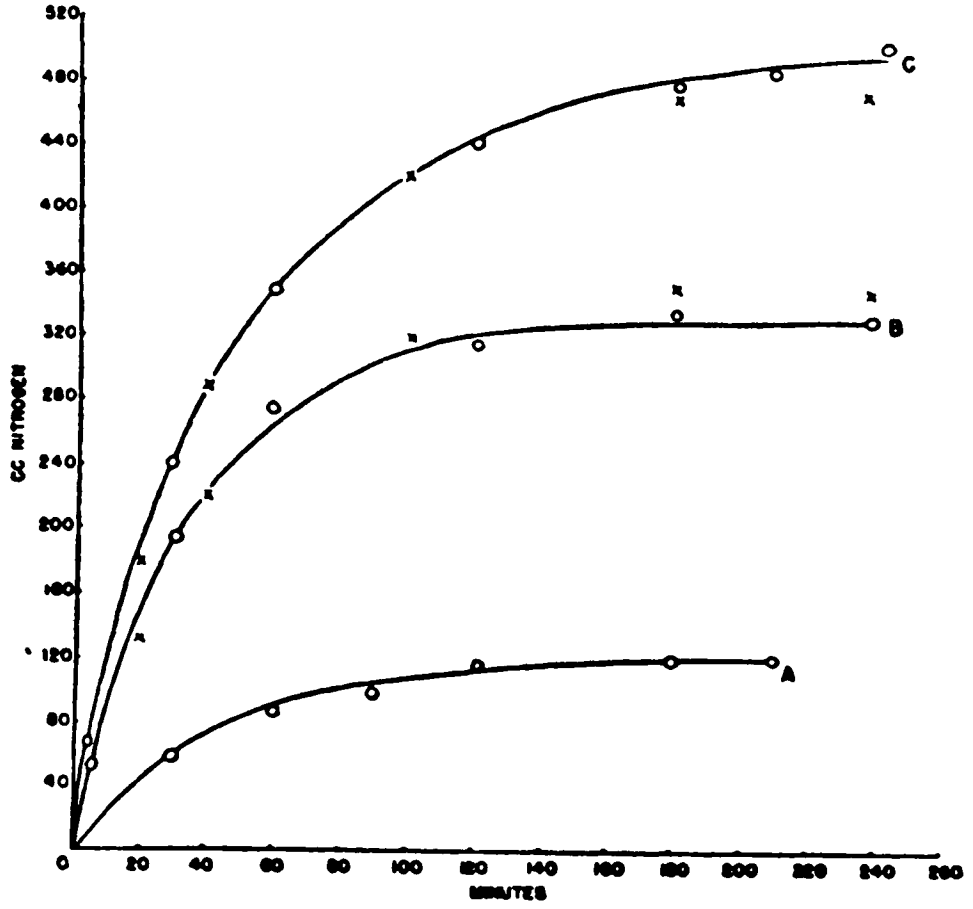


Figure 3.3-4 Nitrogen Elimination of Dog 'D' Following Equilibrium Exposures in Air at 1, 3, and 4 Atmospheres Pressure (From Shaw, et al, Am. J. Physiol., 112:545, 1935)

NITROGEN ELIMINATION AFTER PARTIAL SATURATION AT HIGH AIR PRESSURES; PRECISENESS OF NITROGEN MEASUREMENTS

The dog cannot be decompressed rapidly (within 15 seconds) after equilibration with pressures much greater than 4 atmospheres. At 5 atmospheres pressure, however, for exposures short of saturation, e.g., 75 minutes, rapid decompression is safe, whereas the rapid decompression after an exposure for 90 minutes gives unmistakable evidence of bubble formation, e.g., the increase in respiratory rate to a value of 54 in Experiment 4A, Table 3.3-1.

Experiment No.												Remarks
2	Time*	12	36									Compression 45 lbs/sq in for 4 hrs. followed by decomp. Dog in good cond. the following day.
	Resp. rate	20	20									
	Blood pres.	110	110									
4A	Time*	4	8	14	17	21	25	94	200			Compression 60 lbs/sq in for 1.5 hours.
	Resp. rate	24	22	34	24	50	54	36	19			
	Blood pres.	(values remained bet. 120-130mm Hg										
4B	Time*	3	7	25	33	37	45	46				Compression 60 lbs/sq in for 2 hrs. followed 200 min. after initial compres. (4A)
	Resp. rate	14	14	9	8	7	7	Failure				
	Blood pres.	124	120	140	60	40						
6A	Time*	3	11	14	17	19	21	26	32	36	58	Compression 60 lbs/sq in 2 hours.
	Resp. rate	7	19	20	38	69	78	92	47	17	11	
	Blood pres.	90		112						90	90	
6B	Time*	1	3 Recompression									Compression 75 lbs/sq in for .55 hr. followed 58 min. after initial compres. (6A)
	Resp. rate	9	Failure									
	Blood pres.	64	110 to 25		120	92	88					

*Minutes following decompression.

Table 3.3-1 Relationship Between Nitrogen Bubble Formation, Respiratory Rate, and Blood Pressure in Dogs Rapidly Decompressed from High Atmospheric Pressures

Nitrogen elimination from the same anesthetized dog after partial saturation (75 minutes) at 1, 4, and 5 atmospheres is shown in Figure 3.3-5. It is remarkable (despite inability to make measurements during a lung-rinsing period) that the quantity of nitrogen taken up by the dog's body during the 75-minute partial saturation period is in such good agreement with the amount of nitrogen eliminated during a period of 75 minutes following saturation at the various pressures indicated.

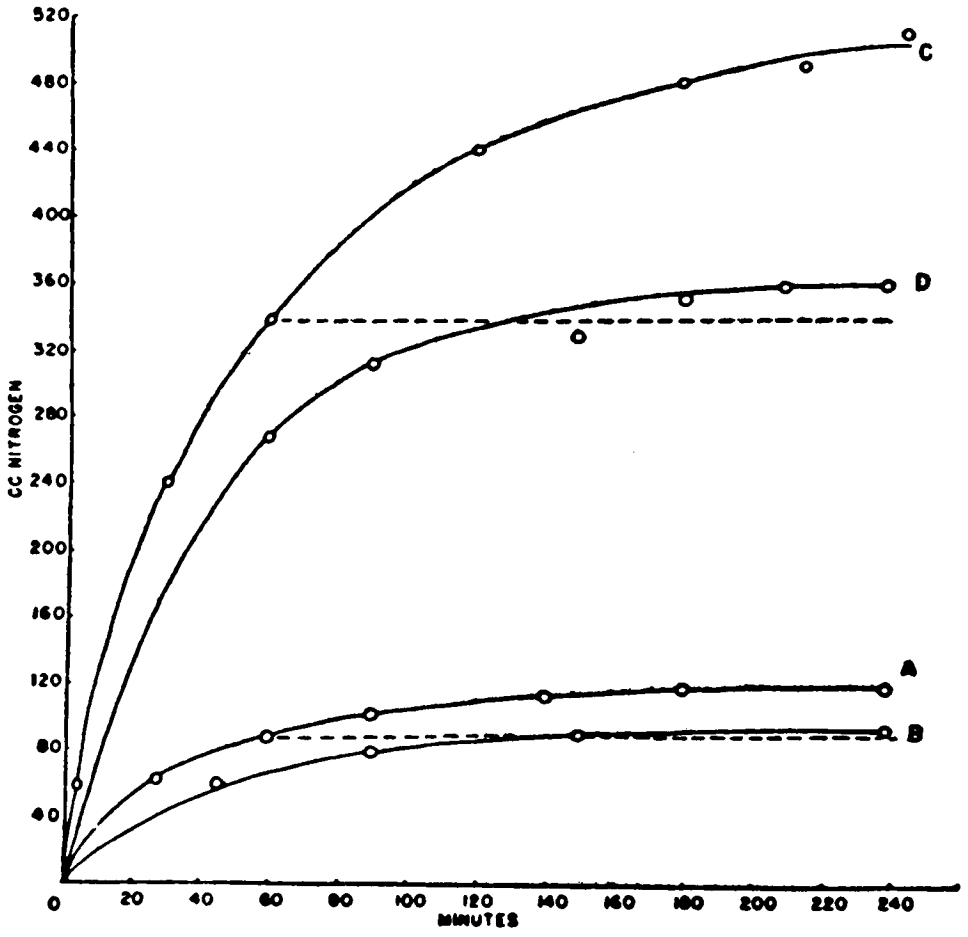


Figure 3.3-5 Saturation Time Compared with Desaturation Time, Dog 'D' (From Shaw, et al, Am. J. Physiol., 112:545, 1935)

THEORETICAL DIVING DEPTHS FOLLOWED BY CONTINUOUS RAPID ASCENT

From the nitrogen elimination curve, Figure 3.3-6, it has been possible to calculate diving depths from which continuous, rapid ascent is possible. Thus, on the principle that if rapid decompression is safe after 100 per cent saturation at 2.0 atmospheres (absolute), then it is safe after 50 per cent saturation at 4.0 atmospheres and 25 per cent saturation at 8.0 atmospheres, or absolute pressure times per cent saturation = k, in this case 2.0. Diving practice has confirmed these predictions, and it has been possible in chamber tests to reach simulated depths of 300 feet (10 atmospheres absolute) under conditions of rapid descent and continuous ascent, i.e., within a total period of about 5 minutes.

THE MANIFESTATIONS OF BUBBLE FORMATION

In the anesthetized dog rapidly decompressed from high pressures (5 atmospheres absolute and 90 minutes or more exposure) there is a characteristic symptom triad, Figure 3.3-7, of slow pulse rate, rapid respiration (tachypnea), and fall in blood pressure. These symptoms appear at a time when circulating bubbles are seen in arteries and veins of subcutaneous blood vessels or when bubbles are present in blood withdrawn from the left ventricle by means of a glass canula inserted into the jugular vein.

In Table 3.3-2 data are present which reflect the severe anoxia, retarded circulation (high a-v difference), and capillary injury (hemoconcentration) when large numbers of bubbles produce stasis in the vascular system.

	Arterial pCO_2	Resp. Rate	%Sat. HbO_2	Blood Pres.	Arterial Venous O_2 Dif.	O_2 Capacity
	(1)	(2)	(3)	(4)	(5)	(6)
Control Period	45	20	90	116	3.6	22.8
Post-Compression Period	59	142	24	140 to 30	6.9	26.1
Recompression Period	56	40	88	90	11.7	27.3
Period Following Recompression	59	125	26	100*	19.6	29.8

*Oxygen was inhaled during the 2-hour recompression period.

Table 3.3-2 Physiologic Effects of Too Rapid Decompression (5-6 seconds) of a Dog Exposed to 65 lbs/sq in Gauge Pressure for a Period of 105 Minutes

RAPID SHALLOW RESPIRATION (TACHYPNIA), A SIGN PATHOGNOMONIC OF BUBBLES IN PULMONARY VESSELS FOLLOWING DECOMPRESSION

Of special interest are the effects on respiration (Tables 3.3-1 and 3.3-3). When, as in Experiment 2, Table 3.3-1, rapid decompression takes place from

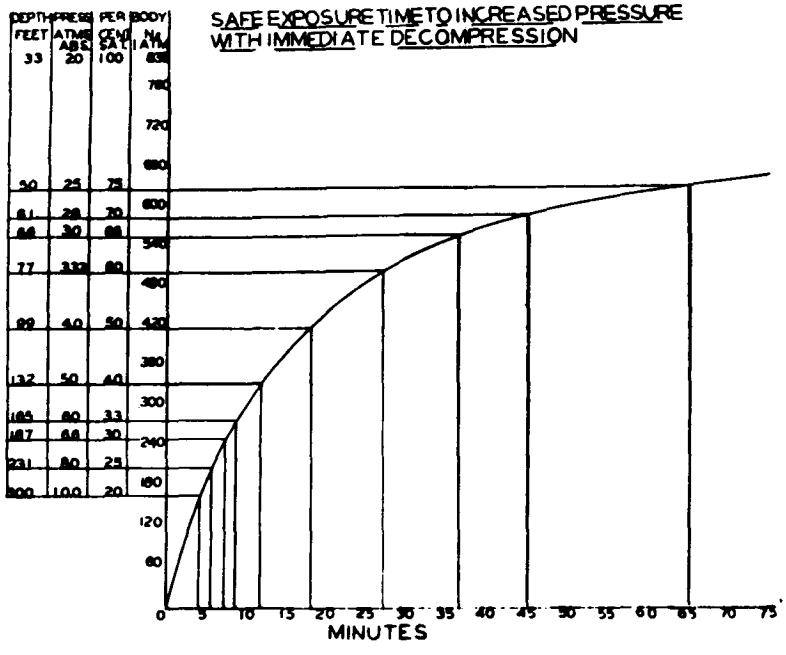


Figure 3.3-6 Safe Exposure Time to Increased Pressure with Immediate Decompression

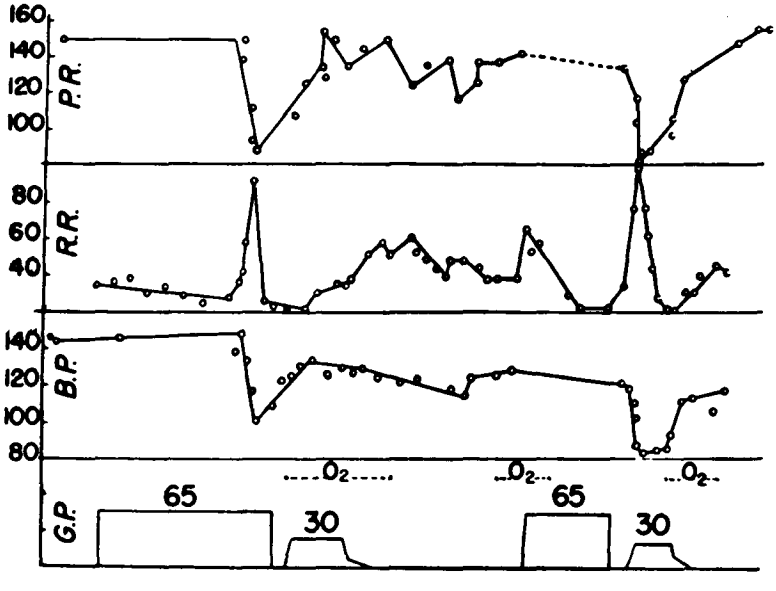


Figure 3.3-7 Alterations in Blood Pressure, Respiratory Rate, and Pulse Rate Resulting from Rapid Decompression

4 atmospheres (absolute) pressure (45 lb/sq in, gauge), the respiratory rate of the anesthetized dog is unchanged. In Experiment 4A, however, rapid decompression from 60 lb/sq in, gauge pressure, was followed by an augmentation of respiratory rate to a value of 54, followed by a return to normal, presumably when the pulmonary bubbles were eliminated. Large numbers of bubbles produce the type of asphyxia first aptly designated by the early caisson workers as "chokes".

Time		Resp. Rate	Remarks
12:22	65 pounds air pressure	26	105 minutes compression
12:33	Following decompression	90	Period of bubble formation, air 1 atmosphere
1:04	Oxygen 30 lbs gauge	20	Recompression
1:10	Oxygen 10 lbs gauge	30	Oxygen decompression
1:16	Oxygen 5 lbs gauge	32	
1:32	Oxygen 1 atmosphere	40	
2:30	Air 1 atmosphere	52	
3:00	Oxygen 1 atmosphere	40	
3:09	Air	40	
3:50	65 lbs air	22	p.p. of O_2 1.12 atmospheres
4:06	Following decompression	100	Period of bubble formation

Table 3.3-3 Relationship Between Respiratory Rate, Air Pressure, and the Inhalation of Air and of Oxygen in an Anesthetized Dog Rapidly Decompressed from High Air Pressure

I have repeatedly experienced rapid, shallow respiration following prolonged exposures in compressed air. Occasionally recompression was necessary to prevent chokes, but on a number of occasions there was a spontaneous disappearance of pulmonary symptoms after several hours without recompression, e.g., as in Experiment 4A, Table 3.3-1.

I have often called attention to a premonitory sign of chokes and probably the earliest sign (on presumptive evidence, but very good indeed) of the presence of bubbles in pulmonary vessels, namely, the sensation of substernal irritation, tracheal dryness, and pain followed by paroxysmal coughing when deep inspiratory effort is made. The inhalation of tobacco smoke by habitual smokers is especially irritating. The fact that the deep inspiratory test has not been applied routinely or even occasionally following decompression of divers and caisson workers or in altitude chambers has led to asphyxial injury and death otherwise preventable had the subject test been employed.

CERTAIN PHYSIOLOGIC AND TOXIC EFFECTS OF OXYGEN

It has been repeatedly observed that pulse rate is decreased in man when oxygen is inhaled at pressure of 1 to 4 atmospheres. Willmon and I have observed a striking "nicotine" reversal of the bradycardia brought about by the inhalation of tobacco smoke which, following oxygen inhalation under conditions of

rest, may increase pulse rate by 20 counts or more.

At 4 atmospheres the bradycardia associated with oxygen inhalation may terminate in syncope or in an increased pulse rate followed by a severe convulsive seizure (Behnke, et al).[67]

Of special interest is the constrictive effect of oxygen on the retinal vasculature, Figure 3.3-8, which gives rise to peripheral amblyopia. In infants inhaling pure oxygen (1 atmosphere) the constrictive effect of oxygen on blood vessels may initiate the development of retrolental fibroplasia leading to blindness.

In a study of the pial vessels of the cat the vasoconstriction was observed when oxygen was inhaled at 4 atmospheres pressure. Most striking, however, was the dilatation of pial vessels when 2 per cent (8 per cent effective) carbon dioxide was added to the oxygen, Figure 3.3-9. The dilatation of cerebral vessels by carbon dioxide (increased cerebral blood flow) can explain the well-known, heightened toxicity of oxygen when pulmonary carbon dioxide tension is elevated.

In a series of elegant experiments by Shaw, et al,[68] the toxicity of oxygen was controlled by artificial hyperventilation and the dependence of oxygen toxicity on the alveolar carbon dioxide tension definitely established. This lowering of alveolar carbon dioxide tension by hyperventilation as a measure to reduce toxicity when oxygen is inhaled would appear to be of practical importance in diving operations.

EXPERIMENTAL OXYGEN DECOMPRESSION IN MAN

By way of summarizing the preceding paragraphs it may be well to present tabular data from experiments of Willmon and Behnke[69] to determine on the basic measurements of nitrogen elimination 1) the optimal level for oxygen inhalation, i.e., if slowed circulation and oxygen toxicity retard gas removal from tissues and 2) the degree of "supersaturation" tolerated following rapid decompression after short exposures in air at 4 atmospheres pressure. The attempt was made to determine whether or not a 'break' in the nitrogen elimination curve or a frank departure from the exponential type of elimination would occur following decompression as drastic as a drop in pressure from 4 to 1 atmospheres within a period of two minutes.

A study of the tabular data, Tables 3.3-4, 5, 6, reveals that in several experiments there were indications of retarded nitrogen elimination either from the adverse action of oxygen or from bubble formation as a result of the precipitous decompression procedure. The experiments, however, are too few in number to permit conclusions, but they serve as a model for future work.

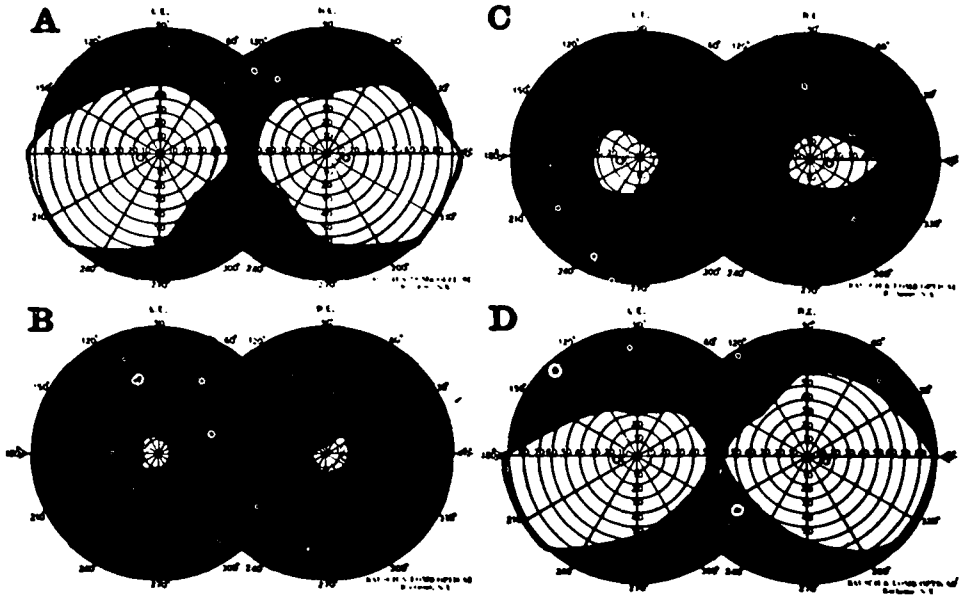


Figure 3.3-8 Perimetric Measurements Made Before and After 3.5 Hours Oxygen Breathing at 3 Atmospheres Pressure (From Behnke, et al, Am. J. Physiol., 114:436, 1936)

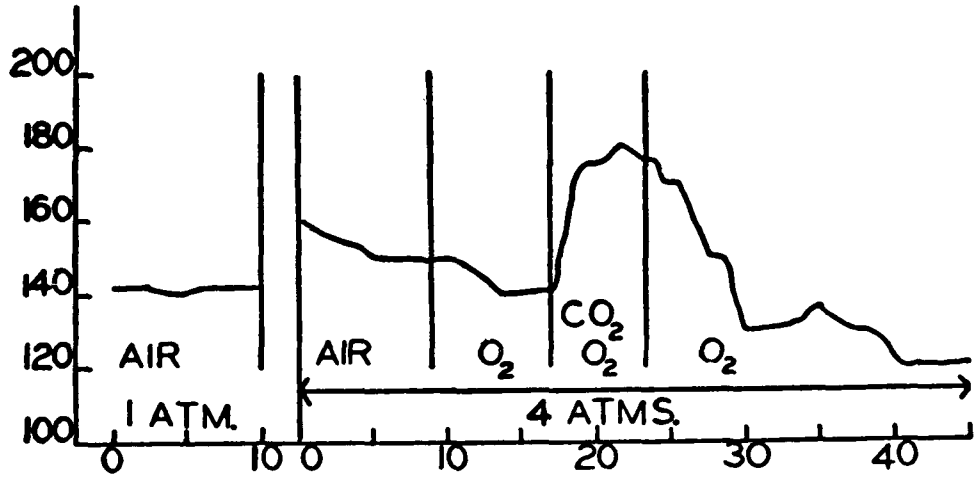


Figure 3.3-9 Effect of Carbon Dioxide and Oxygen on Pial Arterioles (Published in Am. J. Physiol., 111:557, 1935)

STOP	NITROGEN ELIMINATED (cc)					
	At Stop		At Surface			Total
Feet	3-13'	3-30'	33-60'	60-90'	33-90'	3-90'
30	798	1322	728	330	1058	2380
40	831	1335				
50	861	1527	544	430	974	2501
55	1023	1534	430	297	727	2261
60	952	1583	560	354	914	2497
80	817	1463				
90	919	1364				
100	689	1196	967*	374	1341	2537
*Elimination at 50-foot level						

Table 3.3-4 Nitrogen Elimination of One Subject Shown at Levels from 100 to 30 Feet and at Surface, Following Uniform Exposure of 75 Minutes at 100 Feet Simulated Depth

SUBJECT	STOP (ft)	TESTS	NITROGEN ELIMINATED (cc) At Stop 3-30'	Surface 33-90'	Total 3-90'
S	20	1	1478	834	2312
	50	2	1533	957	2590
	100	2	1415	739	2154
Z	20	2	1127	777	1904
	50	3	1220	809	2029
	100	1	849	785	1634
W	20	1			
	50	1	1587	982	2569
	100	1	1486	949	2435
D	20	1	1081	687	1768
	50	1	1079	674	1753
	100	2	1010	754	1764

Table 3.3-5 Nitrogen Elimination of Four Subjects Shown at Levels of 100, 50, 20 Feet and at Surface, Following Uniform Exposure of 75 Minutes at 100 Feet Simulated Depth

STOP	NITROGEN ELIMINATED (cc)		
	At Stop 3-30'	Surface 33-90'	Total 3-90'
0	1191	499	1690
0	892	856	1748
0	1147	511	1658
44	1343	548	1891
50	1312	565	1877
66	1341	522	1863

Table 3.3-6 Nitrogen Elimination of One Subject Shown at Surface, 44, 50 and 66 Feet with Subsequent Surface Measurements, Following Uniform Exposure of 30 Minutes at 100 Feet Simulated Depth

3.4 USE OF NITROGEN-OXYGEN MIXTURES IN DIVING

E. H. Lanphier
Lieutenant, Medical Corps, USNR
Experimental Diving Unit

The necessity for spending considerable amounts of time in decompression has always been a limiting and burdensome factor in diving. At the present time this amounts to a great deal more than an inconvenience. We are confronted by urgent military applications of diving where decompression presents an almost insuperable obstacle unless something can be done to circumvent it.

Since we know that the necessity for decompression in ordinary diving arises from exposure to increased partial pressures of nitrogen while breathing air at depth, one solution to the problem is obvious. We can give the diver a breathing medium which contains less nitrogen and more oxygen than air does. Of course, this approach has its limits. If the partial pressure of oxygen exceeds certain levels, the diver will then be subject to oxygen poisoning -- which hardly represents an improvement in his status. But even with this restriction, the use of nitrogen-oxygen mixtures seems capable of 'solving' the decompression problem in many of the situations with which we are concerned.

When the Experimental Diving Unit undertook the job of formulating tables for the use of various nitrogen-oxygen mixtures, it had to specify depth-time limits for exposure to both nitrogen and oxygen. Consideration of the nitrogen factor was not very difficult. The standard U. S. Navy Air Decompression Table was translated into the nitrogen partial pressures corresponding to the various depths, and conservative interpolations were made where necessary. An electronic computer converted this information into a fine set of tables ready for actual test.

The oxygen limits were not so readily handled since there was no comparable body of information on which to base them. The limits specified had to be very safe since the consequences of oxygen poisoning during a dive are obviously serious. Since exertion greatly reduces oxygen tolerance and since diving certainly involves hard work, the limits had to consider the exertion factor very adequately. On the other hand, making the limits as completely conservative as we might have liked would have eliminated most of the advantage of using nitrogen-oxygen mixtures in the first place.

Neither previous studies of oxygen tolerance during exertion nor field experience with various types of oxygen exposure enabled us to proceed very confidently. Nor were we able to undertake a study in which working subjects would be exposed to oxygen at various pressures until unequivocal signs of toxicity developed and thus derive the limits in this way. Instead, we were obliged to derive a rather arbitrary "limit curve" by educated guessing and to test this as a working hypothesis. The curve is shown in Figure 3.4-1. The ordinate represents actual depth in feet while breathing oxygen, readily converted to partial pressure, and the abscissa represents time. The reason for cutting the curve off at 45 feet and 15 minutes was that going deeper would have put an unacceptable burden on the accuracy of time-keeping in actual dives. In testing this hypothetical

tolerance curve, we attempted to make up for various limitations, such as an inadequate number of subjects, by going 25 per cent beyond the limit curve in exposure time. The 'test curve' which was actually used is indicated by the broken line. Tests were conducted in the range between 20 feet and 45 feet, inclusive, breathing cylinder oxygen on open circuit. The subjects were underwater and were working at rates which approached their endurance for the time involved.

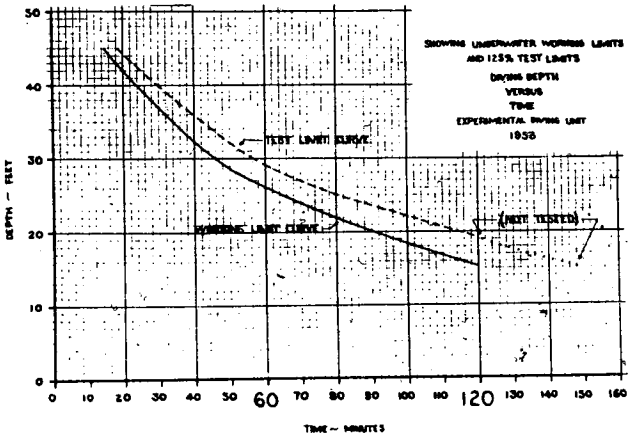


Figure 3.4-1 Oxygen Limit Curve

In these tests one of the rules of the game was that a subject could terminate the run if he so desired, if he experienced symptoms which he considered to be evidence of oxygen toxicity. This rule was unavoidable, and it made it difficult for the investigators to evaluate the significance of minor symptoms which might or might not represent toxicity. Nausea, for example, can indeed be an early symptom of oxygen poisoning, but it can also result from a variety of other causes.

During the study fifty-one runs were made by nineteen subjects. Two major convulsions occurred, both within one minute of the test curve at 35 and 40 feet, respectively. A very near thing with generalized muscular twitching occurred when I tried working at 50 feet for 15 minutes when we were briefly considering tests at greater depths. Four runs were terminated within the limit curve because of 'minor' symptoms which, at the time, most of us did not consider very convincing. At any rate, the proposed oxygen limit curve was accepted pending similar tests using mixtures.

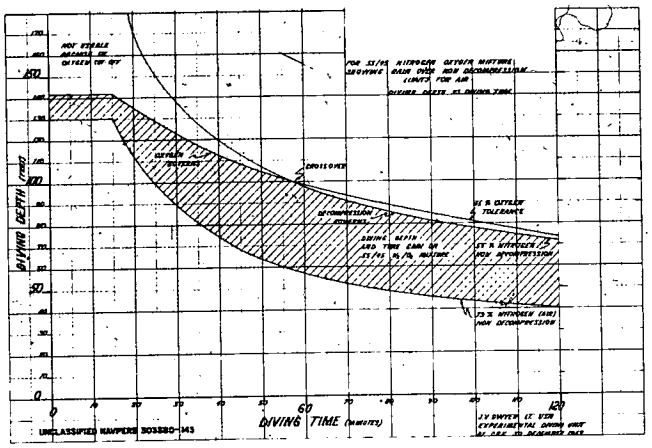


Figure 3.4-2 Nitrogen Nondecompression and Oxygen Tolerance Diving Limits

The curve was fed to the computer, as the nitrogen data had been, and further tables for various mixtures emerged. At this point let us look at the decompression advantages which nitrogen-oxygen mixtures offered and how the various limits interacted. Figure 3.4-2 presents a graphic picture of this for a 55 per cent nitrogen - 45 per cent oxygen mixture. The lower curve is what we call the non-decompression curve for air-diving. Within these limits of depth and time a man can dive breathing air, and return to the surface without decompression stops. (The time includes both descent and actual bottom-time.) Note for example that 15 minutes is allowed at 130 feet, 25 at 100 feet.

The curve coming down from the upper margin represents this same non-decompression curve, here translated into the corresponding limits for a 55 per cent nitrogen mixture. The extension of limits, as compared with air, is tremendous. But the oxygen limit curve, similarly translated for 45 per cent oxygen, cuts off a considerable amount of this gain. At 100 feet, 58 minutes, we reach what we call the crossover point for this mixture. To the left of this point, the oxygen limit applies; beyond it to the right decompression is the limiting factor. If taking a few minutes of decompression at 10 feet on ascent is possible, the diver can go beyond the decompression limit, but he will still be limited by the oxygen curve. Using this mixture on a nondecompression basis has increased the time by only 9 minutes at 130 feet, but has more than doubled it at 100. The gains are even greater at shallower depths as indicated by the shaded area.

This, I should remind you, is the theoretical picture. What happened when we began testing exposures to the mixtures is of more than routine interest. The method was essentially identical to that used in studying the oxygen limit curve, but the results were not very similar. Our first test of this sort involved a mixture containing 47 per cent oxygen, and the depth of the first run was 100 feet. The oxygen partial pressure corresponded to that encountered when breathing pure oxygen at 29.5 feet, or air at about 280 feet. Referring back to Figure 3.4-1, we find that the test curve for this oxygen exposure stands at 58 minutes -- a point reached many times with no symptoms whatever. But on this first mixture run the unfortunate subject had a very convincing convulsion at 20 minutes. As in most of the convulsions we see, there was no warning of any kind. Not even the well-known swings of individual susceptibility could explain this convulsion adequately, and we found no error in our mixture, our depth, or our calculations.

Although we saw no more convulsions, subsequent exposures under the same and similar conditions produced enough other symptoms -- fairly convincing ones this time -- to indicate that we were contending with a reality. A given partial pressure of oxygen was simply proving more toxic in the presence of increased nitrogen pressure. This contradicted everything we had believed about the toxicity of oxygen being directly related to its partial pressure, and we were at a loss to explain our findings.

Only one factor seemed eligible for incrimination, carbon dioxide excess, which is known to have a profound influence on oxygen tolerance. But there was no carbon dioxide in the mixture, and an open-circuit breathing system had been used. If carbon dioxide were involved, it would have to be on the basis of its retention by the body. Several possible causes for such retention are listed in Table 3.4-1, and I will say what I can about them in a moment.

Understandably, the approach to testing our nitrogen-oxygen tables had to be changed in the meantime, but the urgency of providing at least something which the field forces could use prevented complete abandonment of the study. At the present time the Experimental Diving Unit is working up from considerably lower partial pressures of oxygen, checking both the oxygen and nitrogen limits, in order to define the limits within which the tables may still be usable. It is also using additional measurements during these runs in the hope of shedding light on some of the possible mechanisms involved in the observed decrease in tolerance at higher oxygen pressures. It is difficult to predict what the outcome may be. Mixtures

appear to retain considerable advantage in certain limited ranges. It may, perhaps, be possible to extend these ranges by eliminating individuals who are unduly susceptible to the increase in toxicity, whatever its mechanism may be. But it seems likely that the final answer may have to be sought in means other than the use of nitrogen-oxygen mixtures if decompression can really be circumvented at all.

1. Excessive Dead Space (mask. et cetera)

2. Reduction of Respiratory Minute Volume due to

   a. Increased breathing resistance
   b. Increased pO_2
   c. Increased pN_2
   d. Other (?)

3. Alveolar Retention

Table 3.4-1 Possible Causes of Carbon Dioxide Retention During Exertion While Breathing Nitrogen Oxygen Mixtures at Depth

One thing is certain; we are into some extremely interesting physiology. We hope that this symposium may be able to yield some help -- at least advice -- or better yet, actual research either in your own laboratories or in cooperation with us.

In the list of possible causes of carbon dioxide retention, which we feel is the most likely avenue of approach, I have listed dead space first only because it is involved in the one real difference between the oxygen tests and the mixture tests. In order to conserve the mixtures, it was necessary to shift from an open circuit with continuous flow to open circuit with demand. A good commercial diving mask with a demand valve was used for this. This functioned admirably, but the mask does contain some dead space. Although it seems unlikely that the amount involved could make any important difference, this is a factor which requires (and is receiving) investigation.

There is some evidence in need of confirmation but at least not contradicted that respiratory minute volume (RMV) is reduced significantly at least in some individuals when they work at increased ambient pressures. Retention of carbon dioxide might thus result simply from inadequate ventilation. A similar reduction in RMV has also been reported with increased partial pressures of oxygen alone. If this occurs, it must certainly have been operative in our oxygen tests, and the results must take it into account. Some further explanation for the difference encountered in the mixture tests must be sought. There is, in fact, reason to believe that the reduction in RMV during work at depth is greater than can be explained by the partial pressure of oxygen alone.

If depth does cause a further reduction in ventilation, this might be attributed to the increase in breathing resistance which occurs at depth not only in almost

all breathing apparatus, but also in man's own airways. We do not know how much of a reduction this might explain. It may be necessary to ascribe some of the reduction to a respiratory depressant effect of nitrogen itself, although the effect of nitrogen on the sensorium is not very pronounced at the depths concerned. Very likely there are other possible explanations which have not occurred to us.

It may be possible that difficulties in carbon dioxide elimination arise from the increased density of gas at diving depth or related factors, even in the presence of supposedly adequate pulmonary ventilation. Dr. Bean has suggested such a possibility, and it must be considered.

Finally, of course, I should reiterate the fact that the explanation for this phenomenon may not lie in carbon dioxide effects at all. We certainly need help in finding the answer, and I hope the problem seems as fascinating to you as it does to me.

3.5 SOME THEORETICAL ASPECTS OF THE USE OF MULTIPLE-GAS MIXTURES FOR DEEP-SEA DIVING

A. P. Webster
Commander, Medical Corps, USN (Ret)
U. S. Naval Air Development Center

The theoretical aspects of the use of multiple-gas mixtures for diving are somewhat in conflict with the practical aspects. On theoretical grounds, when the deformation pressure, D, surrounding a bubble exceeds some threshold value, D', nerve fibers or endings are stimulated by the mechanical deformation of the tissues and symptoms result. On theoretical grounds, then, the deformation pressure does not depend on what kind of gases are present, but rather on the sum of the partial pressures of all the gases present, see Figure 3.5-1.

Note that the deformation pressure, D, is large when any of the respective partial pressures are large, and in the words of Nims[70] "Decompression sickness would appear irrespective of which gas had the largest partial pressure; and it is only an accident of nature that nitrogen is the gas which is the chief factor

$$P_{N_2} + P_{CO_2} + P_{O_2} + P_{He} + P_{H_{20}} - H = D + \left(\frac{2\gamma}{r}\right)$$

where

P_{N_2}, P_{CO_2}, etc. = partial pressures of the respective gases within the bubble

H = hydrostatic pressure

O = deformation pressure

γ = gas-water interfacial tension of the fluid surrounding the bubble

r = radius of the bubble

Figure 3.5-1 Pressure Conditions within a Bubble

in decompression sickness....." in air. It has been stated that symptoms occur whenever the gaseous pressure of the bubble exceeds the hydrostatic pressure of the tissues by a significantly large amount, that it does not matter what the particular gases in the bubble are, or how the hydrostatic pressure in the vicinity of the bubble is altered. If the deformation pressure, D, is greater than a given critical value, pain results.

Assuming the foregoing remarks to be substantially correct, there are two other main events taking place simultaneously which must be considered: The diffusion of gases from the tissues into the bubble and the desaturation of the tissue gases via the lungs. Both of these phenomena are considered to be exponential with specific time constants. The important point, however, is that the rate at which a specific gas, e.g., nitrogen or helium, enters a bubble may be different for different gases, whereas the time (or diffusion) constant governing the exchange of gas between the tissues and the alveolar air is generally considered to be, for all practical purposes, the same for various gases. And, in fact, this constant has been shown by Jones[71] to be proportional to blood flow through the tissue, and the time constants for the elimination of helium, nitrogen, krypton, argon, and xenon have been shown to be substantially the same.

The rate of entry of gas into the bubble may, however, be largely controlled by the size of the molecule and hence tend to follow Graham's Law, in which the diffusion is proportional to the reciprocal of the square root of the molecular weight. If this is the case, helium would tend to enter a bubble at a faster rate than would nitrogen, and high helium concentrations in the respired gas would tend to prolong the decompression time since rapid entry of gas into the bubble would cause an early approach to the critical deformation pressure, D'.

Figure 3.5-2 shows the advantages and disadvantages of the three gases, O_2, N_2, and H_e.

		ADVANTAGES	DISADVANTAGES
HIGH CONCENTRATIONS OF	O_2	Survival Prolong Dive	Toxicity
	N_2	Rapid Decompression at Shallow Depths for Short Times	Narcosis
	He	Physiologically Inert	Slow Decompression Requires O_2

Figure 3.5-2 Advantages and Disadvantages of Oxygen, Nitrogen, and Helium

One of the questions before us is what is the advantage of a multiple-gas mixture over a single-gas-plus-oxygen mixture. Further, what would be the advantage in using a mixture composed of nitrogen, helium, krypton, argon, and oxygen. Since we do have established decompression tables for air and helium-oxygen mixtures, I have confined the following calculations to helium-nitrogen-oxygen mixtures, as illustrated in Figure 3.5-3.

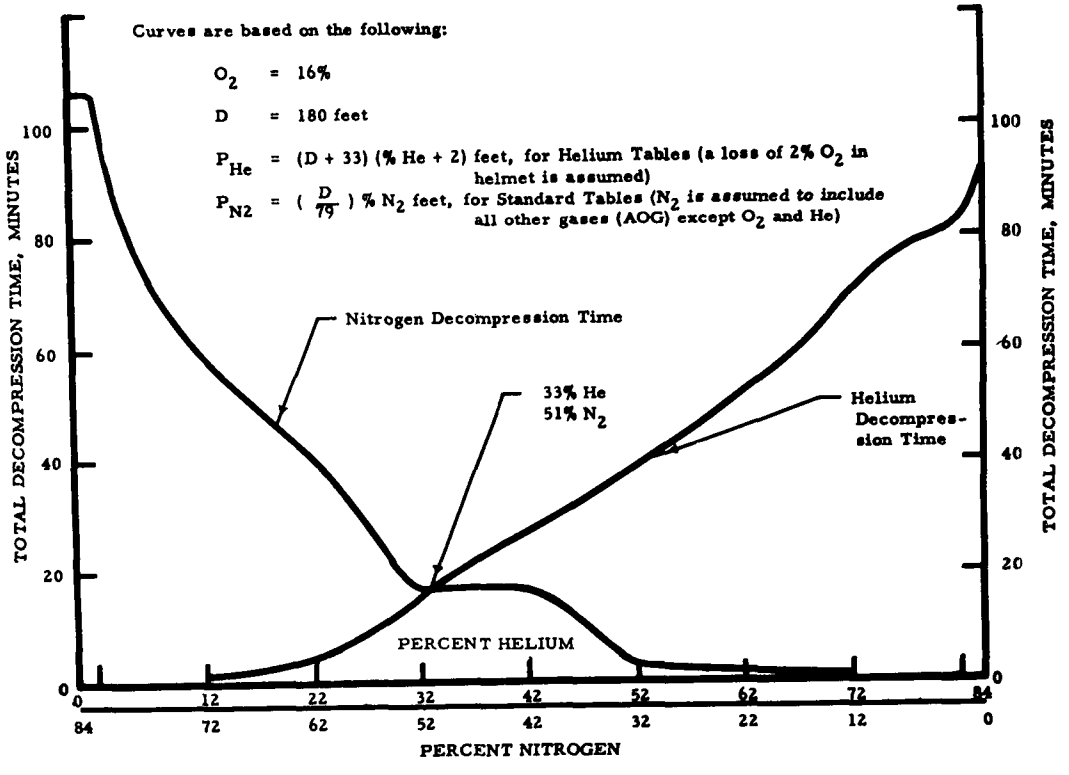
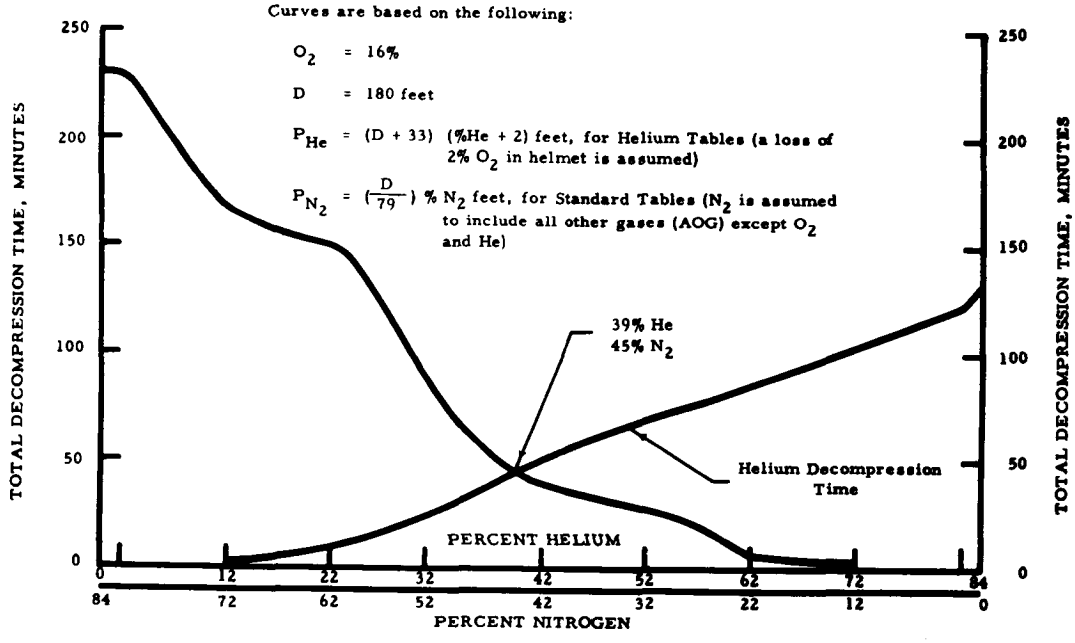


Figure 3.5-3 Theoretical Decompression Times for Dive to 180 Feet for 30 Minutes

These curves were prepared by assuming that a dive is to be made at a given depth, for a given time, and with a given oxygen percentage. For various percentage mixtures of the two gases, helium and nitrogen, the partial pressures of these two gases in the mixture were calculated in feet. Entering the Helium Tables and the Standard Tables,[72] the total decompression time for each gas separately was obtained and plotted.

In order to fit the practical calculations based on the Helium Tables and the Standard Tables into the theoretical framework, one may assume that for both the helium and nitrogen decompression curves, when a mixture of both is used, the critical deformation pressure is just reached at each point along each curve. For the combined gases the deformation pressure is 2D' or twice the critical pressure to produce pain, Figure 3.5-4.



Figures 3.5-4 Theoretical Decompression Times for Dive to 180 Feet for 60 Minutes

Note that the intersection of the two curves for this 60-minute dive is at about the same place as the 30-minute dive.

Figure 3.5-5, an 80-foot dive for 50 minutes, shows that the intersection of the two curves is about where it was for the deeper dive. Note that the intersection of the two curves is at approximately the same percentages of helium and nitrogen.

It is not easy to predict whether any advantage is to be gained using a multiple-gas mixture. If one accepts the thesis that the inert gas helium has its primary advantage in preventing necrosis, and that the gas nitrogen has its primary advantage in requiring shorter decompression times at the shallower depths (or lower partial pressure equivalents), then it is possible to conceive that a mixture of the two may yield some of the advantages of both.

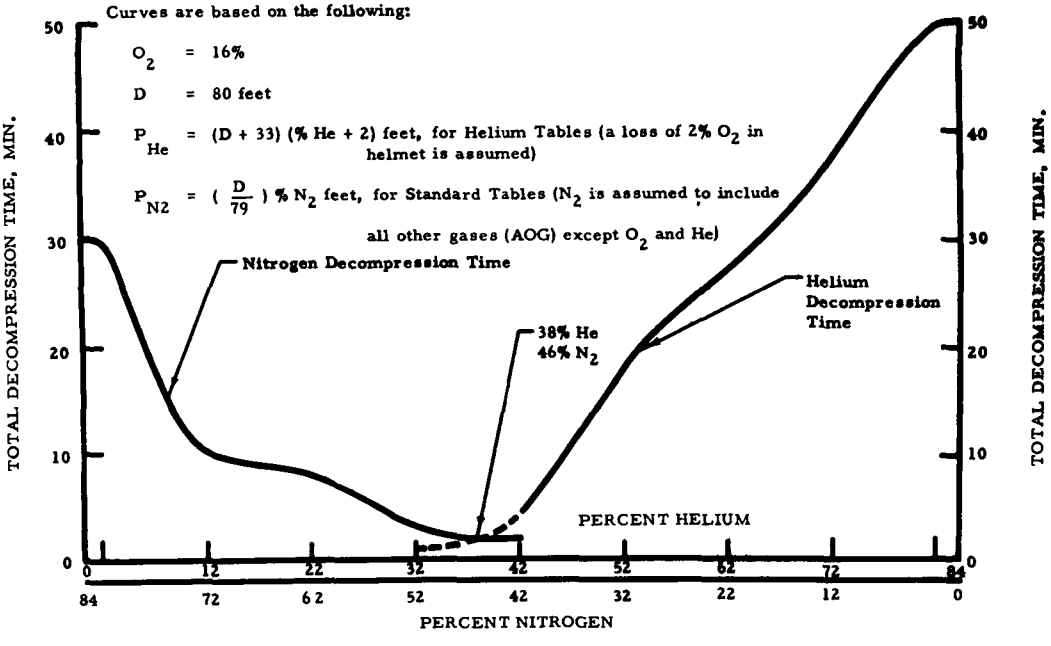


Figure 3.5-5 Theoretical Decompression Times for Dive to 80 Feet for 50 Minutes

3.6 PANEL-FLOOR DISCUSSION OF DECOMPRESSION AND BENDS

Dr. A. R. Behnke, Chairman
Dr. E. N. Harvey
Dr. F. Hitchcock
LT E. Lanphier
Dr. R. Livingston
CDR A. P. Webster

DR. BEHNKE: We should like to have any questions from the floor at this time.

DR. BURTON: I am a bit hesitant as I was very interested in this subject and did some work on it about fifteen years ago, and am speaking merely from memory, but I should like to ask this question. Do you think we really know that the symptoms of pains are due to bubbles? Under my experiences with the aviators, pains presumably are of the same origin, except they are cured by coming down, whereas divers get them when coming up to the surface. Is it the bubbles in the vascular system which are really causing those symptoms? I could illustrate one experiment Dr. Bazett did. If it has not been confirmed, I would like to know, but if it is true, I think it throws a grave doubt on the assumption that it is bubbles in the vascular system which cause the symptoms of pains.

As Dr. Behnke illustrated, the amount of nitrogen left in the body reduces with time, if a person breathes pure oxygen. I think desaturation is down pretty low, certainly in an hour. But there is a very long tail on the curve indicating that there is some left after many, many hours of breathing oxygen. As he said, nitrogen comes down very rapidly in the blood stream, when one breathes pure oxygen, and I suppose in a half hour the blood is pretty free of it.

A number of people in aviation thought one hour desaturation gave protection from bends. If a man were desaturated before he went up and then began to breathe oxygen as he went up, he would not get bends, but I am not sure it was really proved that this did give complete protection.

Dr. Bazett felt that he would like to see what would happen if you completely desaturated a man, so I was one of his subjects. That is the only reason I know anything about this and learned to breathe pure oxygen all night long, eight or nine hours of desaturation, so presumably we were way out at the end of the curve. Then he showed with, I think, a sufficient number of experiments to be specifically valid that this gave complete protection from bends when one subsequently went up in an altitude chamber.

Then he discovered the extraordinary effect that after breathing oxygen all night, one could breathe air for as long as two or three hours and still have this protection. In other words, by breathing air the blood stream must resaturate again very quickly, filling the blood stream full of nitrogen once more; and yet those people did not get bends.

The only explanation to me is it is not the bubbles in the blood stream which are causing the symptoms at all, but it must be the release of nitrogen bubbles in some tissues which are very remote from a fusion point of view.

I think it is really an appalling situation that we still do not know where the critical space is, where these bubbles are that cause the symptoms.

In fact, if one wanted to say, "Oh, I think the symptoms of bends, when you have an ache in your wrist, are central in origin", I don't know if I would have an answer to disprove his idea.

I wonder if anyone has had an amputee who still experiences phantom pain to see whether he experiences bends pain in his wrist which isn't there? I think it is an interesting possibility. I do not say I think they are central, but I do not think we have advanced much in all these years in really knowing what the cause of bends is. True, we know a lot more about bubbles in the blood stream; we know very little about bubbles in tissues.

Some people have taken sections of animals in altitudes, but they made the mistake of bringing them down to high pressure again before they looked to see if there were bubbles. So if there had been bubbles, they were gone.

On the fundamental level this is of such practical importance, perhaps we have been guilty of being content with relative ignorance.

DR. BEHNKE: Anyone care to answer Dr. Burton?

DR. RAHN: I wonder if Dr. Burton would like to exclude chokes from this particular phenomenon?

DR. BEHNKE: That is right. The phenomenon of chokes appears to be somewhat different. If an individual descends to great depths breathing air, the nitrogen dissolves in a water component to the saturation point at the depth pressure. This can come out rapidly on ascent without causing trouble. It is true that there is a slow component also, but if there isn't blockage from bubbles in the blood stream, there should not be trouble resulting from the slow components.

In the matter of chokes the bubbles certainly do occur, and one might say, "Well, now it has been said that chokes are related to bubbles outside of the blood vessels in the lungs", but I really do not know where this could be. We certainly know they are in the lungs for we have withdrawn blood filled with bubbles from the right ventricle.

I believe that in the experiments which Gersh did in decompressing animals to high altitudes, the only bubbles he found were those in the blood stream, with the exception of certain tissues rich in lipids.

At a simulated altitude of 50,000 feet when one applies a blood pressure cuff to the arm and takes the blood pressure, say, a half dozen times, so that the skin of the arm becomes somewhat traumatized, one can feel gas bubbles under the skin apparently released from the subcutaneous fat. There is no pain.

Bubbles may also be present in myelin sheaths, the adrenal gland, and the cortex, which are rich in lipids.

Another interesting thing is the malaise which frequently follows decompression. An individual may feel well but one or two hours later will be down and fall asleep for as much as twenty-four hours. This very interesting type of fatigue may be produced again and again. It may occur prior to any bends and may or may not be associated with mild chokes.

We should like to know the answer in biochemical terms to this very specific type of fatigue, which is looked upon as a warning sign indicative of air bubbles flowing in the circulation or perhaps in interference with some function such as that of the adrenal gland. I dislike invoking the adrenal gland specifically because everything has been attributed to it at some time -- with apologies to Dr. Bean and his fine presentation this morning.

DR. HARVEY: I recall an experiment which was talked about during the war in which men were taken up to a fairly high altitude and developed bends near the knee; X-ray pictures were taken and bubbles were actually shown in the connective tissue near the knee.

I would say usually bends is due to bubbles in the tissues rather than in blood vessels. But as Dr. Behnke said, the chokes would seem to be bubbles in the blood vessels which get caught in the alveolar circulation of the lungs.

The nervous effects have usually been attributed to bubbles blocking blood vessels in the nervous system. However, I would say that bends is more generally due to connective tissue bubbles.

DR. BEHNKE: Of course, Dr. Harvey, there is one point I would like to bring out. In these X-ray pictures of the knees, one couldn't be sure where those bubbles were located.

DR. HARVEY: It was a large cavity of gas. It certainly didn't look like a blood vessel.

DR. BEHNKE: Dr. Gersh has decompressed guinea pigs rapidly, and one could see bubbles. There was a beaded appearance in the blood stream. It was not possible to know if they were within or outside the vessels. Certainly they were gas pockets, but there is no reason to believe those gas pockets gave rise to pain.

DR. BURTON: I want to refer to Dr. Evelyn's work. During the early part of the war he took a number of pictures which showed bubbles in blood vessels and pools of gas in the tissues, but the end result was there was no relation of the appearance of these bubbles in the tissues and the particular pain the subject was having. However, there was plenty of gas, and one could roll the bubbles along the veins which were full of bubbles, but there was no pain there at the time. The pain was somewhere else, where the X-ray showed no bubbles. While there were plenty of bubbles in the circulation, I think it is still uncertain as to the true origin of the pain of bends.

DR. BEHNKE: one thing that has been observed in an arm in which the bends pain is present, one frequently observes vascular phenomena -- a blanching of the arm -- the skin becoming cold and clammy. I wonder if the simple experiment of introducing bubbles in arteries has been done, causing the arteries to be stretched? Is it possible to stimulate sensory endings along arteries which will give sensation of pain due to stretching, or do they not respond in that manner?

DR. BURTON: Dr. Greenfield has recently been doing some experiments, injecting bubbles into arteries of his own and graduate students' arms. He started with oxygen, then became bold and used carbon dioxide and nitrogen. This is an interarterial injection of very small bubbles. An extraordinary thing happened. Something happens to the limb so that there is a "hyperemia", if you want to call it that, an increased blood flow to higher levels than one sees even in full vasodilation, for as long as four or five hours afterward. In some cases there are petechial areas of hemorrhage. The results are really most strange. I am not sure that they have been published, although the experiment has been reported to the British Physiological Society.

DR. HARVEY: Were there any pains as a result of those experiments?

DR. BURTON: I think there were some, but not very violent because they have been continuing the experiments.

DR. BEAN: I wonder if in decompression there isn't the possibility of our overlooking the probability that when you rapidly decompress a person, the pressure in the lungs is very rapidly lowered and that with this sudden drop in alveolar pressure, to what may amount to a partial vacuum, you actually suck some of the gases out of the blood and that this removal may be so rapid that the stimulating effect is dependent, among other things, upon the rate of change in blood gases. I wonder if there isn't the possibility that some of these effects of decompression are due to the rapidity of change in gas tension of the blood, quite aside from bubble formation, immediately following and during decompression. It may not persist for long, but there is the probability that it is significant.

DR. YARBROUGH: I think at least in a few rather sad lung accident cases, we are able to find not only the gas in the intervascular, but in the intravascular spaces within the cranium cavity. There, I think, is a true instance where one can say that the bubble is the offending agent.

DR. PAPPENHEIMER: Do you ever section the vagal nerves in the dogs? I would expect that to remove perhaps this tremendous increase in frequency after you have decompressed.

DR. BEHNKE: Yes, we did that, but I don't remember now what the results were.

DR. PAPPENHEIMER: It is a well-known experiment in physiology to inject starch granules and cause an increase, and it is the obvious thing to do, I would think, to cut the vagus nerve under these conditions.

DR. BEHNKE: Yes, of course, with the starch injections one might say it is due to hypoxia. But here using oxygen, there is another factor, a reflex that is not related to the low oxygen that causes extremely rapid rate, which is far beyond any rate one can induce by low concentrations of oxygen.

DR. PAPPENHEIMER: That is my point. This is the so-called Hering-Breuer reflex which would be eliminated by cutting the vagus venous nerve.

DR. BEHNKE: I think this occurred when the vagus nerves were cut, but that certainly would be an experiment to do.

Dr. Pudenz when he was at the Naval Research Institute, prepared monkeys with lucite calvaria, so it was possible for one to observe cerebral vessels of the brain through the lucite window.

In the one preparation in the film you will see, the monkey was exposed to a pressure of 65 pounds for a sufficient period of time, so enough gas was in the body that when rapidly decompressed, bubbles formed. We have a film showing bubbles moving through the cerebral vessels to give you a little idea of the reality of the movement of these bubbles.

DR. SELLERS: Is it purely a matter of solubility of the various gases that is responsible, or completely responsible, for the bubble formation? In other words, in other gases, such as helium or oxygen, is it possible to check down these bends? Does that follow the physical laws that follow the production of bends?

DR. BEHNKE: Let me think about that a little bit. I will show you some bubbles on the brain. If there are no other questions, I should like to make a brief summary. From the basic work of Dr. Harvey and from the studies on oxygen toxicity, there are one or two things that are immediately applicable, I believe.

For example, if an individual is breathing oxygen, and he experiences symptoms of oxygen toxicity, it might be well for him to hyperventilate to lower the alveolar carbon dioxide tension to a minimum. I think that rests on a firm physiological basis, and we need not say any more.

With respect to minimizing the probability of bubble formation, I think Dr. Harvey's work is very important because for years (caisson) workers and divers were told to exercise during decompression in order to promote the elimination of gas. It speeded up circulation, but undoubtedly the violent movements of stretching and exercising increased the tendency to bubble formation.

4.1 INTRODUCTION TO RESPIRATORY PROBLEMS IN DIVING

Herman Rahn
Department of Physiology and Vital Economics
University of Rochester School of Medicine and Dentistry

I should like to welcome you to the last formal session of this group. For the benefit of those who were unable to attend yesterday I should like to review briefly some of the problems which were discussed and show how the program this morning fits into the over-all picture.

During the discussion of oxygen toxicity the enzymatic, neurophysiological, and endocrinological problems were considered as were the respiratory, cardiac, and circulatory aspects. The session concerned with bends and decompression followed the very nice light motif provided by Dr. Harvey -- "Avoid carbon dioxide and avoid exercise".

In his summary following the discussion of bends and decompression, Dr. Behnke delivered what might be called an impromptu 'State of the Union' message, from which it appears that the outlook for the immediate future is not bright. The physiologists also come under scrutiny.

There are two types of physiologists according to this message, if I interpret it rightly, those who are all right, and the academic respiratory physiologists. The latter are not all right because all their time is spent in abstract investigation.

I would like to plead for more opportunity for physiologists to engage in this type of work. At least occasionally we should have time to do some of this. Practical applied problems cannot be satisfactorily solved without the basic information which results from such effort. When some of the studies which will be presented this morning were undertaken, no consideration of their application to the current problems was given. The evaluation of this work in view of these problems is really an outcome of two things: one, the opportunity to do this basic research, and secondly, the constant stimulus, interest, and support given by the Navy to solve or help solve some of the problems. The first paper to be presented this morning is an excellent example.

There is no general heading for the topics to be considered this morning so each presentation will be followed by a discussion period of ten minutes. Dr. Arthur DuBois will begin the program with his paper on breath holding, to be followed by by Dr. John Pappenheimer, who will consider the dead space problem, and Dr. Jere Mead, who has done some very recent work on breathing resistance. Dr. Frank Carpenter will discuss the problems associated with inert gas, and Dr. Karl Schaefer will tell us about carbon dioxide.

4.2 BREATH HOLDING

Arthur B. DuBois
Graduate School of Medicine
University of Pennsylvania

INTRODUCTION

As far as we know, a person who is holding his breath will have to start breathing again because of a combination of three stimuli to breathing. These are low oxygen tension in the lungs (the arterial blood is in equilibrium with the lung air, but has a 10-second circulatory lag) high carbon dioxide tension in the lungs, and small lung volume. The lung air is compressed when you swim downward, and it is expanded when you swim upward. Therefore, it would be interesting to predict changes in the three factors affecting breath holding. It is possible to calculate these changes during breath holding in a subject at rest at zero or a hundred feet of depth, or in other subjects floating upward from a hundred to zero feet, or sinking downward from zero to a hundred feet. The method requires examination of the theory of alveolar gas exchange and lung volume changes during the unsteady state.

BREATH HOLDING IN AIR

Figure 4.2-1 is a schematic diagram showing a pair of lungs at the start of breath holding, characterized by a volume of alveolar gas about four liters, composed of the following gases:

Oxygen	100 mm Hg
Carbon Dioxide	40 mm Hg
Nitrogen	573 mm Hg
Water Vapor	47 mm Hg
Barometric pressure at sea level	760 mm Hg

The effect of carbon dioxide is to make a person cease breath holding and start breathing again at pCO_2 of 60 mm Hg, even though the other gases and volume of the lungs are normal. The effect of low oxygen is to cause breathing at a pO_2 approximately 30 mm Hg, again with the other factors normal. A small lung volume is a strong stimulus to respiration, whereas a large lung volume tends to inhibit breathing. Certain combinations of these factors that stimulate respiration are of special interest to swimmers. The subject cannot voluntarily hold his breath at a pCO_2 of 50 mm Hg, pO_2 of 50 mm Hg, and normal lung volume.[73] If the pO_2 is 100 mm Hg, a pCO_2 of 60 mm Hg is maximum for breath holding at resting lung volume[73] whereas a pCO_2 of 76 mm Hg at full inspiratory tidal volume, or 37 mm Hg at full expiratory volume will terminate slow, voluntary re-breathing.[74]

Figure 4.2-2 by Otis, Rahn, and Fenn, is a special plot of the oxygen and carbon dioxide tensions in the lungs at the time that a person voluntarily stops holding his breath at resting lung volume. The initial alveolar gas composition

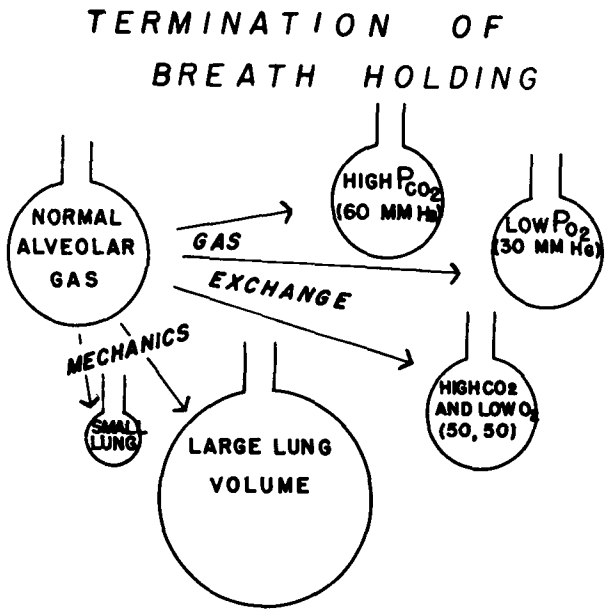


Figure 4.2-1 Factors Influencing Breath Holding Breaking Point (Otis, et al, Am. J. Physiol., 152:674, 1948)

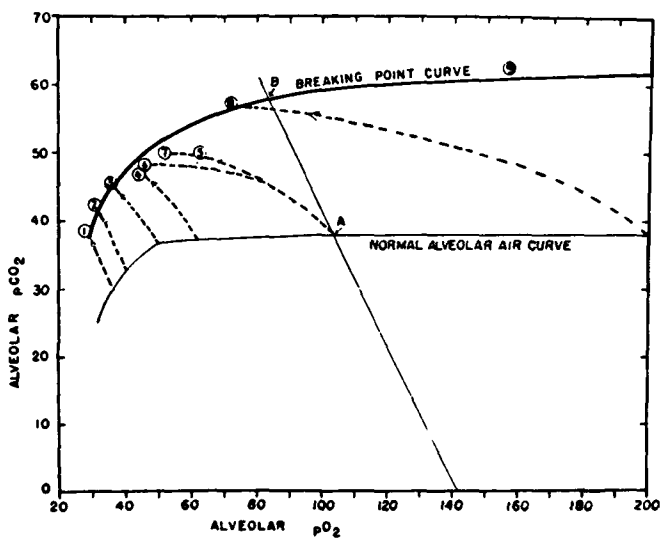


Figure 4.2-2 Alveolar Gas in Breath Holding

was varied by having the subject breathe normally at sea level or at a low atmospheric pressure in an altitude chamber, then hold his breath as long as he could, and finally blow out into a Haldane tube to sample the last part of the expired alveolar gas. The results plotted in this way show the gas tensions at the onset and end of several different experiments. The dashed lines represent the intermediate composition that would be obtained during the breath-holding period. From the diagram you can read intolerable levels of oxygen and carbon dioxide at resting lung volume. Similar experiments have been made at smaller lung volume and larger lung volume by Mithoefer, Stevens, Ryder, and McGuire,(74) permitting them to tell how much carbon dioxide and oxygen are tolerable at different lung volumes.

BREATH HOLDING UNDER WATER

I have used data obtained by Muxworthy(75) and others (76, 77) to show the changes that you should find in alveolar gas if the subject were holding his breath just under the surface of the water or at a depth of 100 feet of water. The carbon dioxide starts at a normal alveolar tension, Figure 4.2-3, and in about 20 seconds it builds up toward a virtual venous tension of about 50 mm Hg. Thereafter, the venous tension gradually rises due to accumulation in the blood stream and lungs of metabolic carbon dioxide. At the same time the alveolar oxygen falls due to the blood flowing through the lungs. Oxygen does not reach venous tension so soon as carbon dioxide because the arterio-venous pO_2 difference is larger than the pCO_2 difference at the onset of breath holding. Furthermore, carbon dioxide may accumulate in the tissues, whereas there is no special storage for oxygen in the body apart from the hemoglobin, so that the metabolic oxygen demand is rapidly reflected throughout the body. (Oxygen debt is also possible.) The net result is that if the breath is held at resting lung volume, the carbon dioxide has risen to 50 mm Hg, and oxygen fallen to 50 mm Hg in about 50 seconds, the swimmer cannot voluntarily hold his breath any longer.

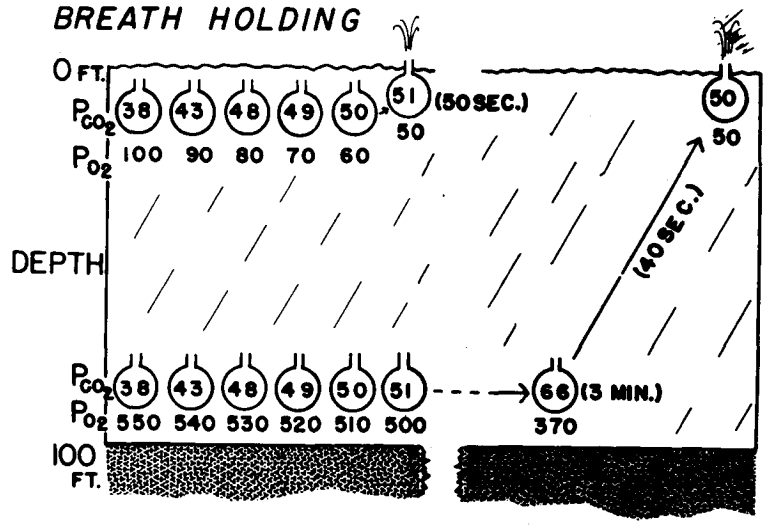


Figure 4.2-3 Effect of Depth on the Composition of Alveolar Gas During Breath Holding

However, at 100 feet of depth, the same subject goes through the same sequence except that the alveolar oxygen tension is much higher to start with because the air in the lungs is compressed to about 4 atmospheres. Therefore, this simulates breath holding on pure oxygen at sea level. The subject can tolerate a much higher level of pCO_2, about 60 mm Hg, because he is fully saturated with oxygen. He can hold his breath about three minutes before the carbon dioxide reaches 60 mm Hg and then he must start toward the surface (see later discussion of free ascent). Indeed Shilling, Hansen, and Hawkins report 216 seconds at 6 atmospheres.[78]

BREATH HOLDING DURING DEPTH CHANGES

The subject who is holding his breath must give up when he arrives at certain combinations of gas tension and lung volume. The timing has been measured experimentally under conditions of rest at sea level and at simulated altitude. In order to understand fully the rate at which these changes occur in lung gas composition, a theoretical analysis has been made to cover the rate of change of alveolar oxygen and carbon dioxide during breath holding at constant ambient pressure.[73, 76] This is extended here to cover changing ambient pressure. Since there are only a few basic relationships, it will be possible to show these equations so that we can predict the alveolar gas composition during breath holding while the subject is floating upward, as in free ascent, or sinking downward, as in a free dive. Two of the basic equations are in Figure 4.2-4. The symbols used in these expressions are those recommended by Pappenheimer, et al.[79] The first equation deals with alveolar carbon dioxide and the second with alveolar oxygen. They represent a combination of the Fick principle which states that the rate of gas entering the pulmonary blood is equal to the arterio-venous content difference times the blood flow, and the relationship:

Rate of change of amount = Rate of change of concentration x Volume.

$$\frac{d\,P_{ACO_2}}{dt} = \frac{(Ca_{CO_2} - C\bar{v}_{CO_2})\,(B\text{-}47)\,\dot{Q}}{V_L + S_{LCO_2}}$$

$$\frac{d\,P_{A_{O_2}}}{dt} = \frac{(Ca_{O_2} - C\bar{v}_{O_2})\,(B\text{-}47)\,\dot{Q}}{V_L}$$

Figure 4.2-4 Equations for Prediction of Alveolar Gas Composition During Ascent and Descent while Breath Holding

These two principles are combined to give the rate of change of alveolar gas tensions as a function of blood flow ($\dot{Q}$), blood gas content (C), standard atmospheric pressure (B), lung volume (V_L), S. T. P. D., and the carbon dioxide 'space' of the lung tissues and capillary blood ($S_{L_{CO_2}}$).

The equations that deal with the effect of changing ambient pressure on alveolar gas composition are given below. Water vapor, of course, is presumed to stay constant, while the other gases in the lung change their partial pressure at a rate proportional to their tension and to the rate of change of ambient pressure (P_B).

$$\frac{d\,P_{A_{CO_2}}}{dt} = \frac{P_{A_{CO_2}}\,d\,P_B}{P_B\quad dt} \qquad \text{and} \qquad \frac{d\,P_{A_{O_2}}}{dt} = \frac{P_{A_{O_2}}\,d\,P_B}{P_B\quad dt}$$

When used in conjunction with the oxygen - carbon dioxide diagram of Fenn, Rahn, and Otis, the expression for the compression or decompression gases becomes simplified as shown in Figure 4.2-5. The subject breathing air at 100 feet begins to hold his breath with alveolar gas composition at point 'A' on the diagram. During ascent this point would follow the diagonal of decompression toward the origin of axes except for the effect of blood flow, which causes an actual pathway shown by the points calculated by combining all the above equations. This particular solution was made so that the effect of decompression in lowering alveolar pCO_2 was just offset by the effect of blood flow on raising alveolar pCO_2.

$$\frac{d\,P_B}{P_B\,dt} = \frac{-d\,P_{A_{CO_2}}}{P_{A_{CO_2(O)}}dt} = \frac{-(B-47)\,\dot{V}_{CO_2}}{P_{A_{CO_2(O)}}V_L} = -K.$$

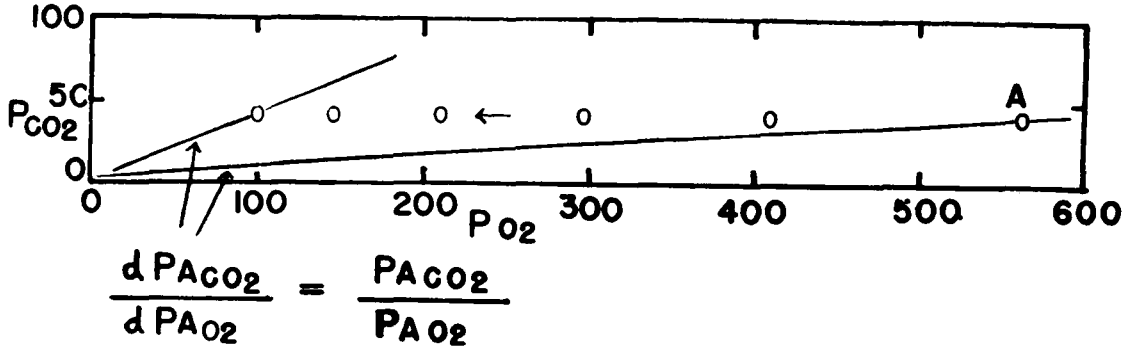


Figure 4.2-5 Simplified Expression for the Decompression Pathway of Alveolar Gas

Integrating and substituting $P_B = \frac{D + 33}{33}$, where D is the depth of water in feet,

$$D = D_{(O)} + 33\, e^{-kt} - 33.$$

Under resting conditions, the value for 'k' was $\frac{(713)(300)}{(40)(4700)} = 1.14$; $D_{(O)} = 100$ feet.

Meanwhile the oxygen is changing according to:

$$\frac{-d\, P_{A_{O_2}}}{dt} = \frac{(B-47)\, \dot{V}_{O_2}}{V_L} + \frac{(B-47)\, \dot{V}_{CO_2}}{P_{A_{CO_2(O)}}\, V_L}\, P_{A_{O_2}},$$

where $\dot{V}_{O_2}$ is the minute volume of oxygen consumption.

The first right-hand term is metabolic oxygen; the second is change in ambient pressure.

Solving and using $\bar{R}$ as the mean respiratory exchange ratio:

$$P_{A_{O_2}} = \frac{(P_{A_{CO_2}(O)} + P_{A_{O_2(O)}})}{\bar{R}}\, e^{\left\{\frac{-(B-47)(\dot{V}_{CO_2})}{P_{A_{CO_2(O)}}\, V_L} t\right\}} - \frac{P_{A_{CO_2(O)}}}{\bar{R}}$$

The numbers substituted were $\left(\frac{40}{.8} + 560\right) e^{-1.14t} - \frac{40}{.8}$

The times shown in Figure 4.2-5 are quarter minute intervals, and depths are 100, 66, 42, 24, 9.5, and -1 foot. These points are also shown in Figure 4.2-6, which represents a subject starting on the bottom at 100 feet of water with normal alveolar air and a lung volume 4.7 liters, as he has just taken a breath preparatory to starting up, breath holding. On the way up he must vent gas from his mouth to prevent overexpansion of the lungs. The alveolar gas composition during the ascent derived from the preceding equations shows a decrease in pCO_2 due to expansion and oxygen consumption, but no rise in alveolar pCO_2 because the expansion just counteracts the metabolic rise as carbon dioxide is brought to the lungs by the venous blood. The net result is that the subject reaches the surface with a normal alveolar gas composition, despite the fact that he has been holding his breath for a minute and a quarter. This seems like a paradox to those of us who have to stop breath holding after a minute on the surface due to the elevated alveolar pCO_2 and lowered pO_2. Of course, if the subject were exercising, he would have to ascend more rapidly or else expect a rise in carbon dioxide and fall in pO_2 as he approached the surface. There is some degree of stability in the system. The rate of ascent should increase as the rate of carbon dioxide production is increased by actively swimming upward. Furthermore, the venous pCO_2 acts as a stabilizing level for the alveolar pCO_2. It is somewhat reassuring to calculate that a subject who is short of breath due to elevated carbon dioxide under 100 feet of water should be re-

lieved as soon as he starts upward and thereby decompresses the alveolar carbon dioxide. There is one danger in this; he may absorb so much oxygen at 100 feet, due to his prolonged tolerance for breath holding that the pO_2 may fall to a low level during the last few feet of ascent approaching the surface. This is shown schematically on the right section of Figure 4.2-3, where the subject ascends rapidly after holding the breath for 3 minutes at 100 feet of water.

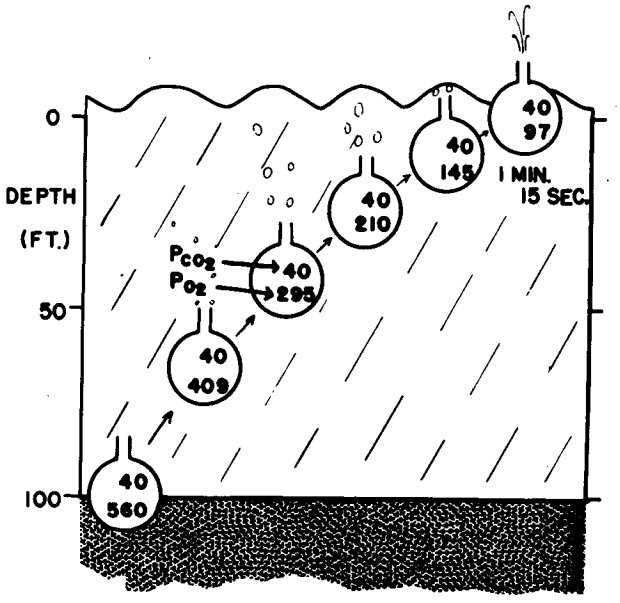


Figure 4.2-6 Alveolar Gas Tensions During Free Ascent

Now if conditions are favorable for breath holding during ascent, how are they for breath holding during a dive downward? The compression of gases in the alveolar space should result in elevation of the pCO_2, which would be additive to the carbon dioxide increase due to metabolism. The lung volume would diminish and act as a stimulus to respiration. The alveolar pO_2 should rise rather than fall because the compression of gases in the lungs exceeds the effect due to metabolic oxygen consumption. The carbon dioxide and oxygen have been calculated by the preceding equations step by step at frequent intervals of depth to obtain cumulative pCO_2 and pO_2 for calculation of each subsequent interval of descent. The essential equation is:

$$\frac{d\,P_{A_{CO_2}}}{dt} = \frac{P_{A_{CO_2}}\,d\,P_B}{P_B\,dt} + \frac{(P_{\bar{V}_{CO_2}} - P_{A_{CO_2}})(S_{b_{CO_2}})(\dot{Q})(713)}{(V_L)}$$

The first right-hand term represents the rate of change of alveolar pCO_2 due to the factor of rate of compression, and the second right-hand term is the rate of change of alveolar pCO_2 due to blood flow. $S_{b_{CO_2}}$ is the physiological dissociation constant of blood for carbon dioxide and has a value approximately 0.5 volumes per hundred cc per mm Hg. $\dot{Q}$ is blood flow in hundreds of cc per second, and 713 is standard barometric pressure minus the partial pressure of water vapor at body temperature.

The capacity of lung tissue for carbon dioxide is sufficiently small to be neglected. The lung volume, V_L, is then given approximately by the expression:

$$V_L = V_{L(O)} \times \left(\frac{33}{33 + D}\right)$$

where D is the depth in feet of water, and $V_{L(O)}$ is the lung volume at sea level. Change in lung volume due to oxygen and carbon dioxide absorption by the blood may be neglected as a small error. Figure 4.2-7 is the solution of this problem for a subject holding his breath descending at 1 foot of water per second to a depth of 100 feet. He is presumed to be at rest.. Note that the alveolar pO_2 is always high, so that there is no danger of anoxia, but that the alveolar pCO_2 rises to a dangerous level of 61 mm Hg at 20 feet, where the rate of compression is rapid. As the depth increases, the rate of compression is less, and the effect of blood flow in taking excess carbon dioxide out of the lungs is greater because of the small lung volume. A given amount of carbon dioxide taken out of a small lung volume decreases the pCO_2 to a greater degree than if it were taken out of a large lung volume.

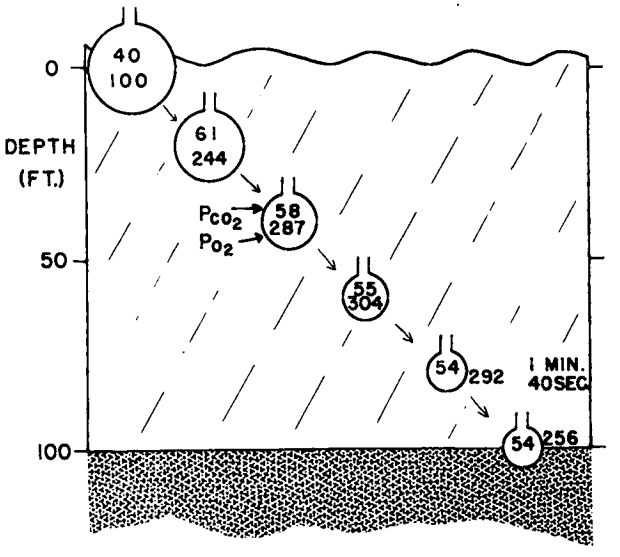


Figure 4.2-7 Alveolar Gas Tensions during Free Dive

As the subject approaches 100 feet, recirculation of venous blood further elevates the pCO_2, and there is also the strong stimulus to breathe caused by compression of the lungs toward residual volume.

A similar calculation of pCO_2 at a rate of descent of 2 feet per second gave a maximum of 69 mm Hg at a depth of 30 feet of water. Exercise would certainly increase the effect of recirculation, similar to its effect in shortening breath-holding time at the surface. However, the increased blood flow might tend to accelerate removal of the carbon dioxide from the lungs if the carbon dioxide were to rise above venous tension due to compressional effects.

CONCLUSION

There are certain commonly known ways of prolonging breath-holding time. These should apply particularly to a person who expects to swim downward or hold his breath while swimming horizontally. The first way is to hyperventilate prior to holding the breath; second is to start with the lungs full of air, and third is to rest before starting breath holding and to use weights to go down or buoyancy to come up, whenever possible, to diminish the rate of metabolism. Some people tolerate a higher pCO_2 than others, as demonstrated by Dr. Karl Schaefer.[80] The data and calculations in this discussion do not deal with hyperventilation or unusual tolerance, but are aimed at the aspects of metabolic rate, blood flow, lung volume, changing ambient pressure and average human tolerance for low oxygen, high carbon dioxide, and altered lung volume.

DR. SCHAEFER: I was quite surprised to see theoretical computation of the alveolar pathways of carbon dioxide and oxygen come so close to our actual examination. There are only a few changes there. When you measure the alveolar carbon dioxide and oxygen prior to the dive, then at 90 feet, and after the dive, there will be a few changes far different from the theoretical computation. The alveolar carbon dioxide starting at the beginning with hyperventilation will be lowest (25 mm Hg), and oxygen will be highest, 125 mm. At 90 feet we find carbon dioxide at about 43 mm Hg, not around 50 or so, and the oxygen pressure is on the order of 200 to 300 mm Hg. Otherwise the whole trend in the development of alveolar carbon dioxide and oxygen tensions is similar to the one described by Dr. DuBois. Similar small changes occur during ascent. I will refer to that in my talk.

DR. RAHN: Thank you, Dr. Schaefer. I was very glad to see Dr. DuBois produce the theoretical results and Dr. Schaefer, last year, produce the practical results.

As I recall, Dr. Schaefer, if you could start off with a pCO_2 of 40 mm Hg, you would go all the way down to 90 feet, and come all the way up, spending a minute and a half doing it, and at the surface your carbon dioxide tension would be less than the carbon dioxide with which you started. Is that correct under certain circumstances?

DR. SCHAEFER: That is right under the condition that you have fast ascent.

DR. RAHN: Now we have exactly the set rates which Dr. DuBois has so nicely figured out for us so that we can go through any gymnastics, theoretically ending up with any alveolar gas concentration we desire.

DR. BEHNKE: I would like the answer to this problem which came up in connection with the work of Ferris a couple of years ago. An individual is under water holding his breath. Now I know the increase in his weight is the result of the utilization of oxygen. It doesn't give one the respiratory quotient, but one gets oxygen consumption practically. In other words, the carbon dioxide is not diffusing into the alveoli.

DR. RAHN: That is right. Carbon dioxide is diffusing in, but at a lesser rate than oxygen is being taken out. Because respiratory exchange is in the lung rather than at the tissue level, the exchange ratio is immediately changed as soon as one holds his breath and goes from 0.8 to something less than this value within a few seconds. The net result is a progressive decrease in total chest volume during breath holding.

DR. BEHNKE: I mean is that true also while holding one's breath under water?

DR. RAHN: Yes, that is right.

DR. BEHNKE: One doesn't get a measure of the respiratory quotient, but practically of oxygen consumption. Is this correct? Has Ferris' work been checked?

DR. DUBOIS: Yes, Dr. Behnke, I have checked it and measured alveolar oxygen and carbon dioxide with breath holding. The factor you mentioned is entered into these equations, that is, the factor that the carbon dioxide rapidly approaches venous level and tends to stay there whereas the oxygen keeps on being consumed, so that you essentially have oxygen consumption after the first ten or fifteen seconds. That factor is in the equation.

DR. BURTON: I was wanting to get to the practical. I would like to be told the equation of the rate in which you must come up to keep the carbon dioxide constant. Could you tell us what this actually means as to determining the rate at which you come up, and how does that correspond with the natural rate, driven by flotation forces? Does one have to fight the natural tendency to changes in flotation forces as you come up, or is it the opposite?

DR. DUBOIS: Dr. Burton, I have little practical experience with this, but what the equation means is that you start out at 100 feet with the rate of ascent something like two feet a second and end up at the surface with the rate of about one foot a second. The total time coming up would be a minute and a quarter. You come up more slowly at the top because your rate of expansion of gases is more rapid. You are expiring gas on the way up because coming from a hundred to zero feet, the gas volume would expand four times. If you started with four liters, you would overextend your lungs so that as you breathe out on the way up, you tend to keep a constant volume. That is what I assume in this equation.

Therefore, I don't see that the rate would accelerate or decelerate the stability. You would have to control this yourself. If you hold your body closed, of course, the lung expanding would give you an acceleration because of the bigger gas bubble in your chest.

The actual times coming up, I do not know. I would have to ask the people from the diving unit as to how long they ordinarily take coming from the bottom to the surface. The actual terms due to exercise, if you double the metabolism, would allow you to come up in half the time, keeping the carbon dioxide tension normal in the lungs. The other factor is that you can still stay down quite a long time and come up more slowly because the oxygen tension is so high that you can tolerate a rather high carbon dioxide until you get right near the surface. You have quite a wide range of tolerance there.

I would like to draw that equation, if I may, on those coordinates.

$$\frac{dP_{A_{CO_2}}}{dt} = \frac{P_{A_{CO_2}} dP_B}{P_B dt} \quad \text{and} \quad \frac{dP_{A_{O_2}}}{dt} = \frac{P_{A_{O_2}} dP_B}{P_B dt}$$

DR. PENROD: I would like to know if the neurophysiological curiosity of the suppression of the desire to breathe by swallowing reflex is of sufficient magnitude to be of any practical significance in this.

DR. SCHAEFER: We have recently measured the differential pressure in the mouth when the diver goes down. We can record whenever the person swallows going down. We found in some people there is quite a different pattern. Some people who have a great desire to suppress it, go down to 50 feet without swallowing, and others swallow continuously. There is this desire to prevent swallowing depending on the person. I think the man who went 150 feet and didn't equalize is one of the worst divers we have.

DR. PENROD: Well, the swallowing isn't necessarily an equalizing reaction for reasons I have never understood, but when you have a very considerable desire to breathe at the breaking point, if you swallow, you of course temporarily suppress the desire. It is an old trick used at times to approach that point. With a mouthful of saliva, one may swallow small (aliquots) and increase breath holding time.

4.3 THE RESPIRATORY DEAD SPACE

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Harvard Medical School
Harvard University

The magnitude and properties of the respiratory dead space are often important factors to consider in the design of breathing apparatus. In particular this is true of open systems, for in this case the economy is directly related to the respiratory minute volume, and this in turn is dependent upon the respiratory dead space. The volume of inspired gas which actually reaches the lung alveoli with each breath is equal to the tidal volume minus the dead space. Given a total dead space of 250 milliliters and a respiratory frequency of 20 per minute, the amount of gas wasted will be 5 liters per minute at 1 atmosphere, 10 liters per minute at 2 atmospheres, and so forth. Of course, the conducting airways which go to make up the personal dead space serve useful functions in filtering, warming, and moistening the inspired gas, but from the point of view of economy of breathing, they are so much waste space. We may think of this respiratory dead space as a sort of compromise on the part of the Great Engineer.

Our problem has two parts. The first part concerns the physiological dead space, its magnitude and variation with exercise, breath holding, resistance to breathing, et cetera. The second part concerns the tolerable limits of added external dead space which inevitably accompany the use of masks, valves, or rebreathing equipment in respiratory apparatus.

First, let us consider the physiological dead space. It is convenient to think of the physiological dead space in terms of two components. The first component is associated with the volume of conducting airways in series with the alveoli, and this we shall call the series dead space. The second component consists of alveoli which are adequately ventilated but poorly supplied with blood. These are in parallel with the well-perfused alveoli and go to make up the parallel dead space.

The two types of dead space have very different properties; for example, the series dead space is relatively independent of the tidal volume, whereas the parallel dead space increases in proportion to the tidal volume, or more accurately, in proportion to the difference between the tidal volume and the series dead space. In healthy individuals breathing under normal conditions, the parallel dead space is extremely small, but it may become appreciable in diseased lungs or in abnormal conditions such as pressure breathing or resistance to gas flow which involve the pulmonary circulation. Failure to consider the series and parallel components separately under such circumstances has sometimes given rise to confusion in the literature. Our principal concern today is with the series dead space in healthy individuals.

How do we measure the series dead space? All of the alveolar gas reaching the atmosphere must pass through the series dead space, and this provides the basis for the well-known Bohr equation in which the dead space is expressed in terms of the tidal volume and the difference in composition between inspired, ex-

pired, and alveolar gas. Measurements of tidal volume and of inspired and expired gas composition are unequivocal, but those of you who are familiar with the physiological literature of the past forty years will be fully aware of the difficulties encountered in assigning any particular value to the alveolar phase. To the professional respiratory physiologist, the subject is likely to be a highly emotional one. But I hasten to add that I am only an amateur in the field. I will discuss two out of the several approaches to the problem, these two being in my opinion the most useful from both the theoretical and practical points of view.

The first involves the dynamic analysis of expired gas and is illustrated in Figure 4.3-1, taken from recent work done in Comroe's laboratory.[81] Here the expired carbon dioxide concentration is recorded simultaneously with the expired gas volume. If the respiratory system were an ideal two-compartment system, carbon dioxide concentration would have risen abruptly when the expired volume exceeded the dead space. In fact the change in composition is distributed in time, and the best one can do is to choose a mean value from which to estimate the effective dead space. The composition continues to change even at the end of expiration and no single portion of the expired gas can be considered representative of the mean alveolar component. The concentration of CO_2 in end-expiratory or in Haldane-Priestley samples is higher than the mean and substitution of these values in the Bohr equation may lead to erroneously large estimates of the dead space, particularly at large tidal volumes. The dynamic method illustrated in Figure 4.3-1 was pioneered by Schoedel in Germany.[82] Schoedel used hydrogen as the test gas. In this country various methods for the rapid analysis of nitrogen, carbon dioxide, oxygen, and other gases have been developed and applied to the problem.[81, 83, 84]

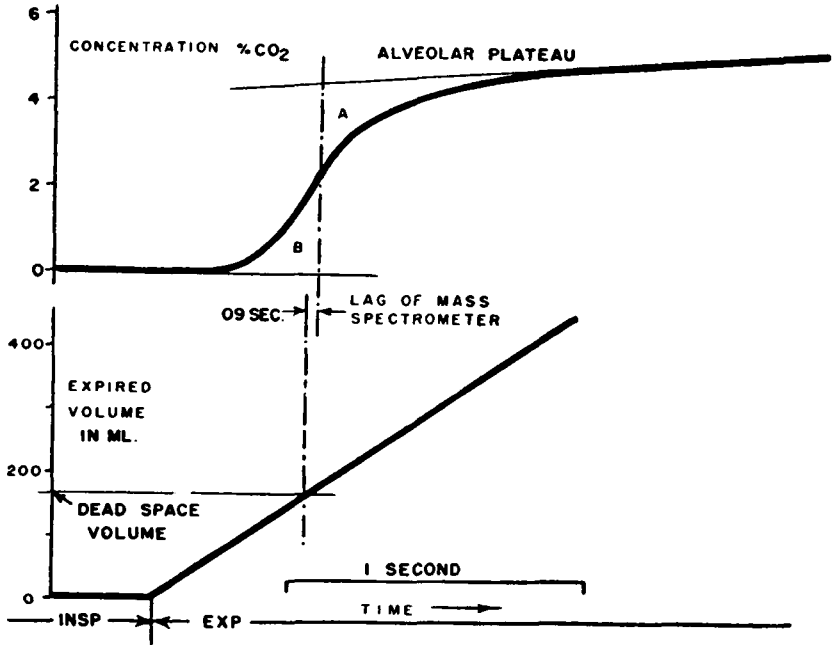

Figure 4.3-1 Illustrating the Dynamic Method of Estimating Respiratory Dead Space (From Bartels, et al, J. Clin. Invest., 33:41, 1954).

Another approach to the problem has been developed in our laboratory[85] and this method is well suited, I think, to the solution of several practical problems relating to the dead space. We suppose that the elusive quantity called mean effective alveolar gas composition will be the same at any tidal volume and frequency, provided that the composition of arterial blood remains the same. In practice this involves breathing at various tidal volumes and frequencies which are regulated in such fashion as to maintain constant the oxygen saturation of the blood in the steady state of respiratory exchange. The subject breathes in time to a metronome and adjusts his tidal volume at any given frequency until the Oximeter reaches a certain value. The sensitivity of the method is greatly increased if one works in the steep part of the oxygen dissociation curve where a change of 1 or 2 mm Hg oxygen pressure will produce an easily detectable change in saturation. The Oximeter is simply used as a sensitive null indicator for constant alveolar ventilation at any given tidal volume. Under these conditions the expired gas composition turns out to be a linear function of the tidal volume as shown in Figure 4.3-2 or 3. At infinite tidal volume the dead space would be negligible, and one would expect the expired gas composition to be the same as alveolar. The effective alveolar gas composition is therefore obtained by extrapolation to the ordinate where V_T is infinite as shown in Figure 4.3-2. This particular experiment was done on a dog in which blood samples could be easily taken to verify the extrapolation.

In a similar series of measurements on normal human subjects Fishman[86] has shown that the extrapolated values for alveolar carbon dioxide average about 1 mm Hg less than the simultaneously determined values in arterial blood. At the other end of the scale when tidal volume approaches dead space volume, there should be no respiratory exchange and the composition of expired gas should be the same as inspired. The dead spaces are therefore measured by the intersections on the inspired gas levels as shown in Figure 4.3-2 or 3. I do not suppose for a moment that the experimental points would in fact fall on the same straight line at these extremes of tidal volume. Thus at very low tidal volumes and high frequencies of breathing, we know from the work of Comroe[87] and others that the dead space may be effectively reduced by incomplete washout, and at the other end of the scale while at very slow respiratory rates, we may expect from the work of Schoedel,[82] Fowler,[83] Forster,[81] DuBois,[84] and others that the dead space may be reduced as a result of respiratory exchange with gas in the bronchial tree. Over the normal range of tidal volumes, both at rest and during light exercise, the effective values of alveolar gas composition and respiratory dead space must be very close to the extrapolated values. Note also from Figure 4.3-2 or 3 that the oxygen and carbon dioxide dead spaces are about equal. This result was never obtained by the older methods, but has been fully confirmed by the dynamic methods of analysis using the mass spectrometer.[81]

When external dead space is added to the system, the extrapolated values for dead space increase in proportion to the added dead space as shown in Figure 4.3-3. Of course, in this case the alveolar values remain unchanged because the subject regulates his breathing throughout in order to maintain the same oxygen saturation in his blood. In the example of Figure 4.3-3 the initial series dead space was 200 ml, but this included some 30 ml in the mouthpiece and valves, leaving 170 ml for the subject's personal dead space. The subject weighed about 170 pounds so that his respiratory dead space was 1 ml per pound body weight.

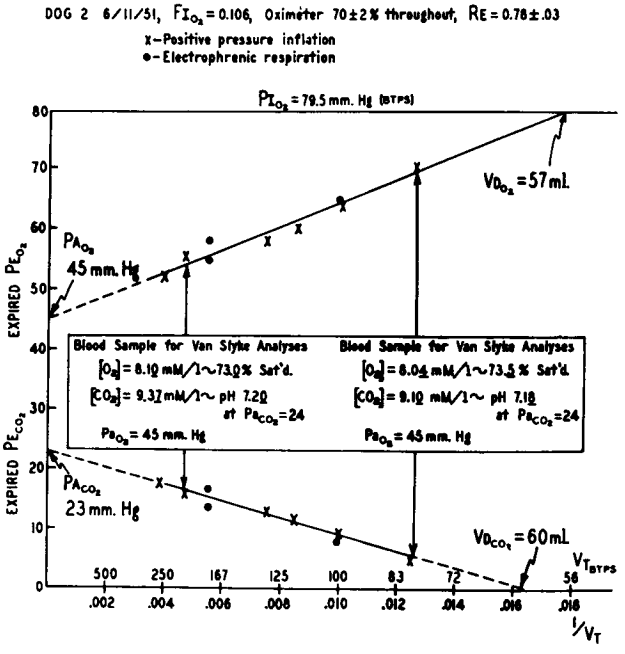

Figure 4.3-2 The Constant Alveolar Ventilation Method as Applied to the Anesthetized Dog

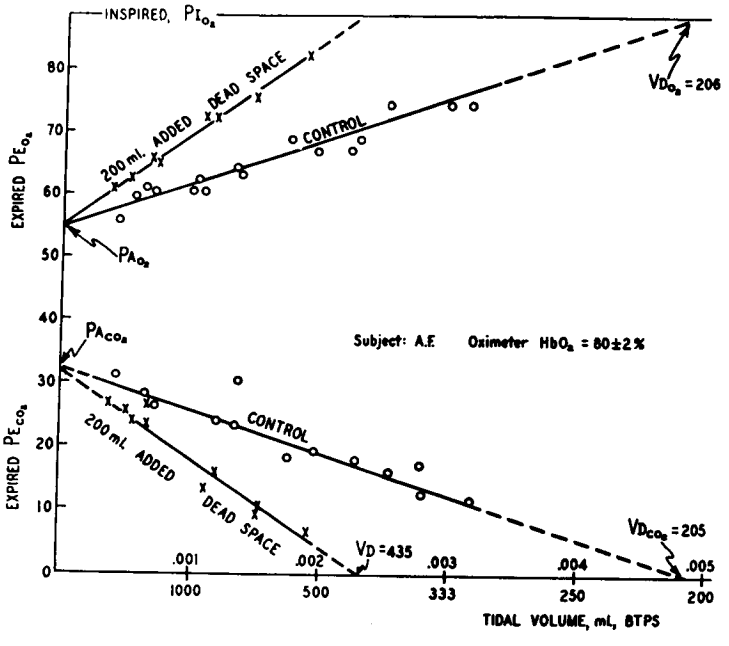

Figure 4.3-3 The Constant Alveolar Ventilation Method as Applied to Normal Man

Radford[88] has recently reviewed data relating dead space to body weight and has found that the figure of 1 ml per lb holds pretty well from babies weighing 9 pounds to adults. It would appear that at long last we have found a rational basis for the English system of weights.

With the aid of the constant alveolar ventilation technique, Dr. Bjorn Folkow and I have recently tried to answer several questions about the dead space. The first question concerns the effects of lung distension caused by positive pressure breathing or by expiratory resistance to gas flow. Figure 4.3-4 shows the effects of varying the mean transpulmonary pressure on the total dead space in anesthetized cats. By transpulmonary pressure I mean the pressure difference between the bronchial tree and the pleural space. It is clear from Figure 4.3-4 that the dead space is sensitive to pressure -- the total increase being about 50 per cent when the lungs are distended by a transmural pressure of 20 cm of water. Much of this increase with lung volume can be accounted for by the intrapulmonary dead space, that is, by the dead space within the bronchial tree below the bifurcation of the trachea. Figure 4.3-5 shows the

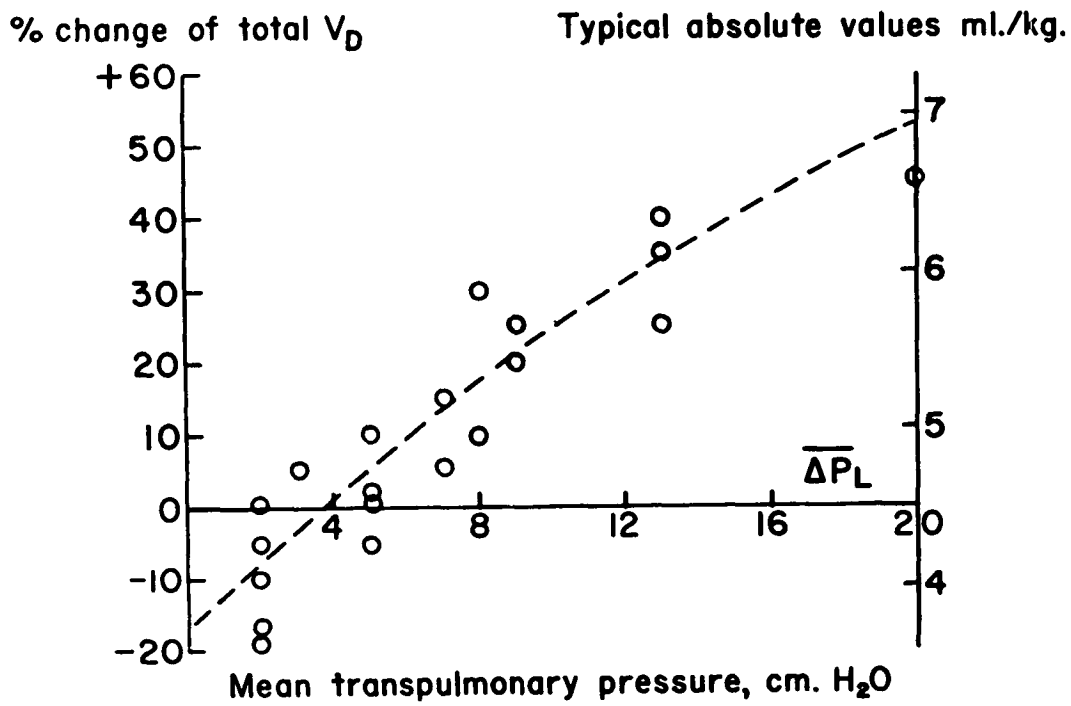

Figure 4.3-4 Effects of Pressure Breathing on Respiratory Dead Space in Anesthetized Cats (From Folkow and Pappenheimer, Unpub.)

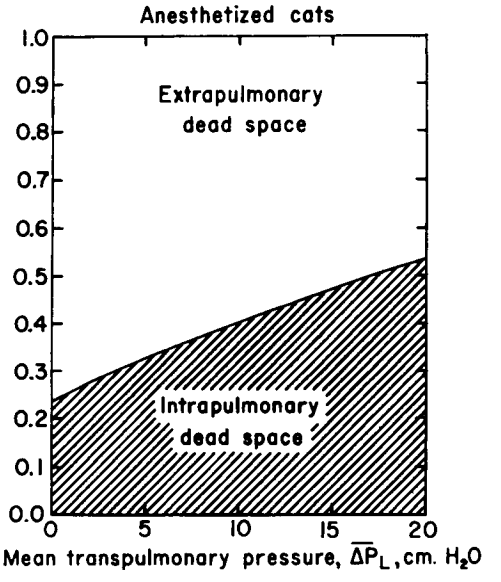

Figure 4.3-5 Proportion of Dead Space Contained within the Lungs (From Folkow and Pappenheimer, unpub.)

proportion of the dead space contained within the lungs as a function of the pressure. The fraction of intrapulmonary dead space at each pressure was obtained by subtracting the volume of the trachea and larynx from the total measured dead space. In a few instances the results were confirmed by measuring the decrease in dead space following ligation of one lung. We conclude that about one third of the physiological dead space is normally located within the lung itself, and that this proportion rises to about one half when the lungs are distended.

The effects of pressure may be readily demonstrated in man. Figure 4.3-6 shows the effects of breathing against 20 cm of water. The series dead space was increased by 125 ml or about 50 per cent of the subject's normal personal dead space. Note also that the alveolar gas composition required to maintain constant oxygen saturation was substantially altered -- quite a different picture from the simple effects of an added series dead space such as that shown in Figure 4.3-3. This, I think, is a result of interference with the blood supply to the alveoli during pressure breathing. The same picture can be produced in animals when the circulation to parts of the lung is occluded. From the change in alveolar values we can, in fact, predict quite accurately the degree to which the circulation is occluded. Thus, in the example shown in Figure 4.3-6, the change in alveolar gas composition was that expected if the circulation to 10 per cent of the alveoli had been occluded. The net increase in dead space, due both to the increase in series dead space and the development of a parallel dead space, was considerable; at normal respiratory frequencies the subject had to breathe at least 25 per cent more in order to maintain a normal blood composition. The development of a parallel dead space during pressure breathing is of direct interest to those interested in oxygen equipment for aviation, but is perhaps not of direct interest in underwater physiology. I wish to raise the question, however, as to whether a parallel dead space can develop as a result of bends. It seems reasonable to suppose that air emboli in the pulmonary circulation would create a parallel dead space, which could be investigated quantitatively by the methods I have described.

I turn now to a brief consideration of the effects of added dead space. In our experiments we have always regulated breathing by means of an Oximeter so as to compensate exactly for the added dead space. There is evidence from the older literature, however, that compensation is a normal physiological response, even without an Oximeter to guide one. Liljestrand[89] in 1918 investigated the effects of added dead space on the tidal volume when the frequency of breathing was maintained constant. The steady state values which he obtained are plotted in Figure 4.3-7. It will be seen that the tidal volume increased in proportion to the added dead space up to 1 liter or more. The alveolar pCO_2 tended to increase

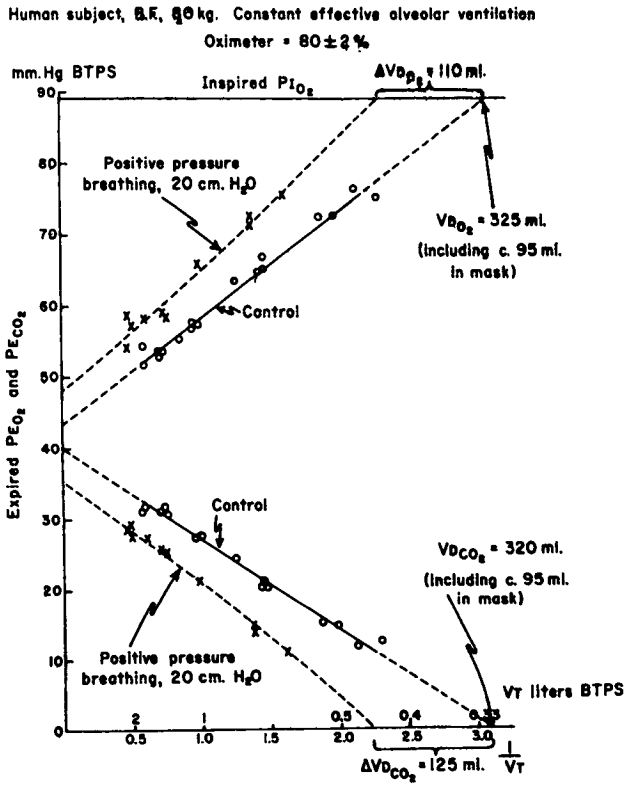

Figure 4.3-6 Effect of Pressure Breathing on Respiratory Dead Space (From Folkow and Pappenheimer, unpub.)

slightly, reflecting a slight increase in carbon dioxide production due to the increased work of breathing at high tidal volumes. It is this rise of alveolar carbon dioxide which evidently supplied the stimulus for sustained increased tidal volume. A few similar measurements have been made by Russ and Stannard[90] and by Millikan,[91] who found, as did Liljestrand, that added dead space up to about 1 liter caused a quantitative compensatory increase in alveolar ventilation. In all cases, however, the experimental conditions were artificial and limited to rest or light exercise. It would seem well worth while to re-examine the problem more carefully under conditions in which the oxygen consumption could be varied over a wide range (exercise). From the point of view of underwater physiology the oxygen concentration in inspired gas should also be considered as a variable which is likely to affect the physiological response to external dead space.

SUMMARY

We may summarize our present concept of the dead space with reference to Figure 4.3-8. The personal dead space is made up of two components, one in series and one in parallel with the functional alveoli. The series dead space is associated with the conducting airways and normally amounts to about 1 ml per pound of body weight. It is relatively independent of the tidal volume at normal frequencies. It increases with lung distension, reaching about 150 per cent of its normal value when the lungs are maximally inflated. The most distensible part of the series dead space is located in the bronchial tree below the bifurcation of the trachea. This intrapulmonary fraction of the dead space is normally about one third of the total and is available for respiratory exchange during breath holding. The parallel dead space, consisting of well-ventilated but poorly perfused alveoli, is normally negligible. An appreciable parallel component may, however, develop during positive pressure breathing or during other procedures which interfere with the pulmonary circulation. The parallel dead space varies in proportion to the difference between the tidal volume and the series dead space. The question may be raised as to its importance during pulmonary air embolism (bends and chokes).

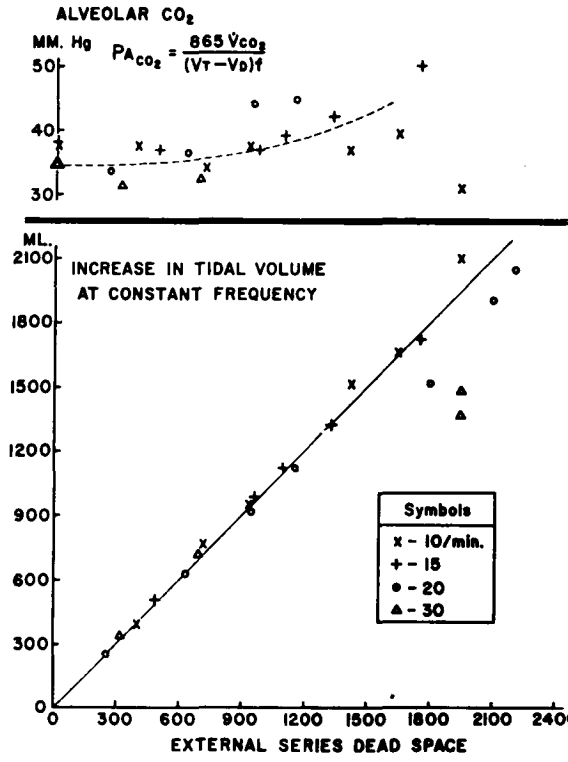

Figure 4.3-7 Effects of External Dead Space

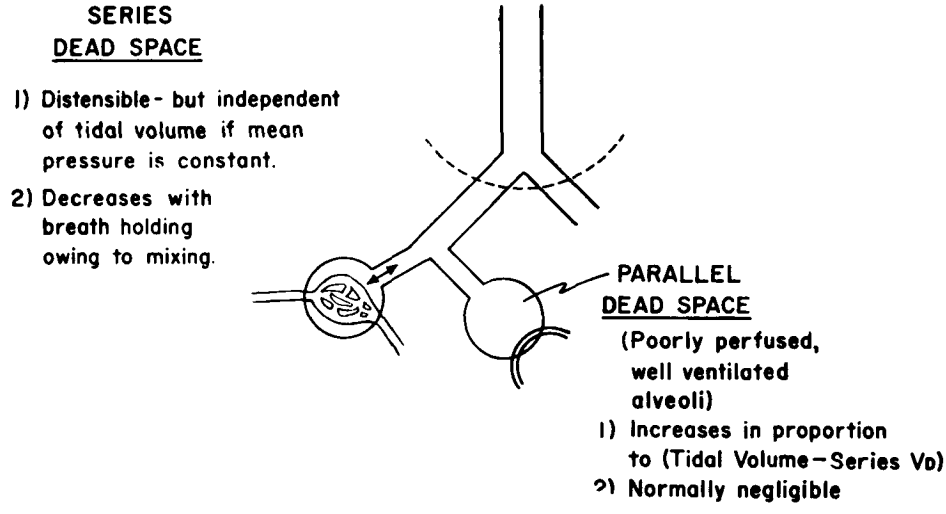

Figure 4.3-8 Schematic Representation of Series and Parallel Dead Space

COMMENTS

DR. RAHN: I would like to ask Dr. Pappenheimer about his last experiment which he cited on pressure breathing. I think this is a fascinating finding, and if I interpret that correctly, this would mean then that if a submariner tried to escape and was building up by improper ventilating at positive pressure, he would be shunting blood from his normal course in the pulmonary circulation into abnormal courses, and if one would visualize it on an all-or-none basis, this would mean that maybe the upper lobe would receive suddenly no blood, while the remaining cardiac output was shunted to the lower lobe. This, of course, is extreme.

Is this interpretation more or less correct?

DR. PAPPENHEIMER: I don't mean to imply that the circulation is completely occluded in any specific region, but there is merely a change in the profusion ratio.

DR. RAHN: Yes. This brings up a very interesting problem. We have some of our mechanical respiration men around. Where in the lobe is the pulmonary circulation occluded by pressure breathing? Is it peripherally, do you think, or evenly distributed?

DR. PAPPENHEIMER: I think I would ask Dr. Mead.

DR. RAHN: Dr. Mead?

DR. MEAD: Who shall I ask? I have no guess at all. What is your guess?

DR. RAHN: Would you like to pass the buck to Dr. Otis?

DR. OTIS: The positive pressure breathing would make it more difficult for blood to get back to the heart.

DR. RAHN: But you would not visualize differential occlusion?

DR. OTIS: I wouldn't know what you mean.

DR. MEAD: At an increased lung volume there should be a slight reduction in the gradient from inside the capillary in the alveoli to the outside, which might tend at a given point to make the capillary smaller and increase the resistance to a very small degree, to the extent that the heart pumping from a given direction would separate further from the alveolar pressure as the lung is inflated.

But this should be a small effect, and who is to say what the distribution would be except as hydrostatic factors might enter into it.

DR. RAHN: You would visualize it in terms of increasing the gravity head by distending the lung.

DR. MEAD: The separation afforded by the elasticity of the lung in the stretch, in effect, puts the pump at a little distance from the lung.

DR. OTIS: I think it would be interesting to know how much of this pressure breathing effect can be attributed to the pressure itself and how much, presumably, to an increase in lung volume.

One should do the experiment not with pressure breathing, but by breathing with the lungs in a very highly inspiratory position all the time to see if the dead space increased there also.

DR. PAPPENHEIMER: This is separating dead space using two components. There is an increase due to the volume.

DR. RAHN: That is a series dead space.

DR. OTIS: I don't know if this parallel dead space is due to the change in volume of the chest or the effect of pressure per se.

DR. DUBOIS: You might think the blood flows through the pulmonary capillary bed easily and slowly so that a little pressure may expand it. But actually it flows in spurts, as shown by nitrous oxide absorption. The distribution of blood under these conditions would be rather hard to predict. I think you have to study the head of pressure and conversion between the kinetic and the potential energy in the system. It might be fairly complex.

DR. RILEY: I am sure there are all sorts of complexities, but just the reduction in cardiac output in itself, I think, would tend to make distribution a little less good because you know that at rest, in the upright posture, the apices are relatively poorly circulated compared to the bases and with larger blood flow, there would be more to the apices. The whole bed would be opened up and with less flow, I think, there would be a tendency to increase the relative underperfusion of the apical areas. This introduces hydrostatic factors and fits in very nicely with some of Dr. Burton's ideas for other organisms, I believe, of critical closing pressure, closing off the ones with the least pressure in them.

DR. BURTON: This hydrostatic factor is really considerable. There is 15 mm difference between the apices and the bases. It is a really considerable effect, so that if somebody asked me to guess where this shutting off or lowering of the ratio of circulation to ventilation in the alveoli took place, I would naturally say it would be in the apices.

DR. BEHNKE: The last topic that Dr. Pappenheimer referred to was of considerable interest -- increasing the dead space, increasing the tidal volume, I believe. What about the minute volume?

DR. PAPPENHEIMER: These data were from Liljestrand. What he did was that he maintained the frequency constant and observed the change in tidal volume.

DR. BEHNKE: In the early part of the war we thought we might conserve

oxygen breathing by just adding a tube, not realizing at first what we were doing. Now, if one inhales oxygen, are there any differences in the relationships from those you presented? Have you repeated the Liljestrand experiment?

DR. PAPPENHEIMER: Other than the adding of dead space to prove the method, I have not done it at all.

DR. WENDELL: I would like to ask Dr. Pappenheimer a question. Is it correct that at a given tidal volume, a change in the dead space results in a change of the Hb-saturation of the arterial blood?

DR. PAPPENHEIMER: Yes.

DR. WENDELL: How then can you measure (a change of) the dead space if you keep it constant by keeping the Hb-saturation constant?

DR. PAPPENHEIMER: No. My point is, if you breathe against a positive pressure, you have to breathe much more to keep the saturation the same.

DR. WENDELL: I am thinking of the method in general. To keep the Hb-saturation constant, doesn't this necessarily result in a constant dead space?

DR. PAPPENHEIMER: That does remain constant over that range of tidal volume. One varies the frequency of breathing and adjusts the tidal volume until the saturation is the same. From that the dead space can be calculated.

4.4 RESISTANCE TO BREATHING AT INCREASED AMBIENT PRESSURES

Jere Mead
Department of Physiology
The Harvard School of Public Health

Some forty years ago, Rohrer[92] suggested that the relationship between the driving pressure and the resulting flow of gas in airways of the lungs could be expressed as follows:

$$\Delta P = K_1(\dot{V}) + K_2(\dot{V})^2$$

where ΔP expressed the driving pressure, $\dot{V}$ expressed the flow of gas, and K_1 and K_2, respectively, were the laminar and turbulent constants of the expression. The first constant included the viscosity of the gas flowing as well as the geometry of the tubular system, while the second constant included the density of the gas flowing and the geometry of the flow system which pertained to turbulence. In considering the total flow resistance of the lungs, an additional factor is necessary for flow of tissue must occur as well as flow of gas. For the moment we shall neglect this additional factor of tissue resistance and examine Rohrer's expression as it applies to the problem at hand.

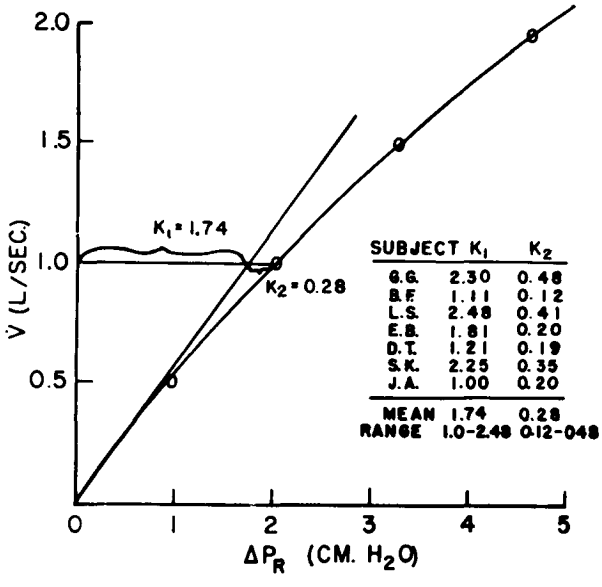

Figure 4.4-1 Mean Resistance Pressure as a Function of Flow for 7 Normal Subjects

The curved line in Figure 4.4-1 represents the mean pressure flow characteristics of the lungs observed in seven normal subjects. A graphic solution of Rohrer's constants was made at a flow of 1 liter per second, and the open circles represent points derived from Rohrer's expression. The derived points offer an excellent fit to the observed curve.

With these data we can attempt a prediction of the influence of the viscosity and density of the gas breathed on pulmonary flow-resistance. Since K_1, the constant which includes gas viscosity, is large as compared to K_2, the constant which includes gas density, we would expect that the changes in gas viscosity should have a greater influence on resistance than changes in gas density. This prediction can be tested by making measurements of pulmonary flow-resistance while breathing various mixtures of gases with viscosities and densities different from that of air. Pure helium, saturated at body temperature, is about one fifth as dense as air and only slightly more viscous. Ethane, on the other hand, is a gas of approximately the same density as air, but one half as viscous. On the basis of Rohrer's expression, pure helium should have a relatively small influence on pulmonary flow-resistance, while ethane might be expected to have a much larger influence.

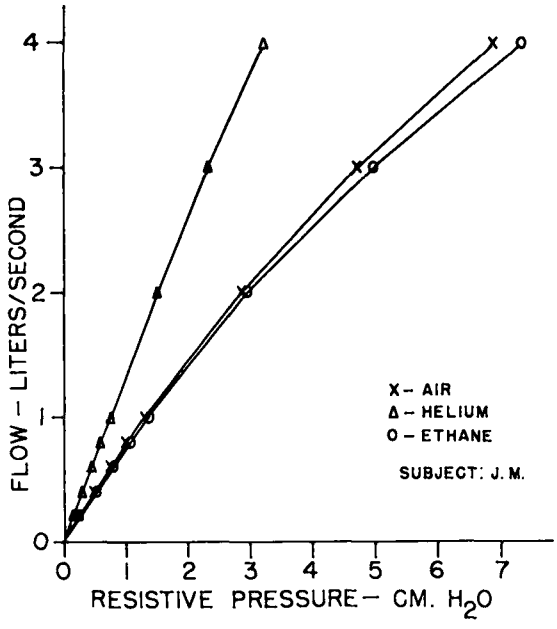

Figure 4.4-2 Flow-Pressure Curves for a Subject Breathing Air, Helium, and Ethane

Figure 4.4-2 shows that our prediction was incorrect. Pulmonary flow-resistance measured during single inspirations of pure helium is markedly reduced, while ethane, which should actually reduce pulmonary resistance, appears to produce a very slight increase in the pressure necessary to produce a given flow rate.

In attempting to explain the contradiction which is present, we must return to Rohrer's underlying assumptions. He assumed all the flow in the respiratory tree to be laminar, except for turbulent eddying at points of cross-sectional change and at bends and turns of the air passages. Gaensler[95] has pointed out that Rohrer was incorrect in his calculations of the critical velocities in the respiratory tree. Taking this error into account, it is probable that turbulent flow exists in the 'tubes' as well as at the cross-sectional changes and bends, and therefore we must examine the factors which influence this additional turbulence.

The tendency to turbulence is expressed by a dimensionless number first described by Reynolds, which includes the radius of the tube, the linear velocity of flow, and in addition, the viscosity (μ) and density (ρ) of the flowing fluid.

$$\text{Reynolds' Number} = \frac{\gamma \times \text{Vel} \times \rho}{\mu}$$

It may be seen that if the density is reduced, other factors remaining constant, the tendency to turbulence is decreased. In contrast, if the viscosity is reduced, the tendency to turbulence is increased.

Reductions in density should reduce the total turbulence in the respiratory tree at a given flow, while reductions in viscosity should have the opposite effect. It would be expected then that reductions in gas density alone should have two effects, both tending to reduce the pressure necessary to produce a given rate of flow. In contrast, reductions in gas viscosity alone should have separate effects that would tend to be self-canceling. In regions of laminar flow, less pressure would be required to produce a given flow rate, but at the same time there would be less laminar flow in the respiratory tree at this flow rate. The results with ethane show that this latter effect actually predominates, so that the flow-resistance is actually slightly increased.

If it is true that the physical properties of the gas influence the topography of turbulence within the respiratory tree at a given flow rate, the geometric attributes of Rohrer's constants, K_1 and K_2, are in reality not constants. Rohrer's expression will not suffice if we are to attempt prediction of the influence of ambient pressure on the resistance to breathing, for in this instance gas density alone will be changed, and accordingly, the distribution of turbulence at a given flow rate can be expected to change. As we shall see, we shall have to settle for an empirical prediction; but before this will be possible, we need to know something about the tissue resistance of the lungs.

From further examination of Reynolds' number it may be seen that if the ratio of density to viscosity is kept constant, the distribution of turbulence, although we may not know what it is, should be the same at a given flow rate. If both the density and viscosity of the gas are reduced proportionately, the pressure necessary to produce a given flow rate of gas should be reduced in proportion to the change in density or viscosity. This follows from the fact that whatever the individual terms of the total pressure-flow expression might be, the sum of the exponents of density and viscosity in the individual terms would in every case be one. Thus, although we do not know the complete expression for gas-flow resistance within the respiratory tree, we can nevertheless predict the influences of changing the gas physical properties on the gas-flow resistance if we take care to keep the ratio of density to viscosity constant in the gas being breathed. For example, if both the density and the viscosity of the gas are one half that obtained for air, the pressure overcoming gas-flow resistance within the lungs should also be one half that observed while breathing air at a particular flow rate.

If in the total flow-resistance of the lungs, tissue resistance plays a role, we have the means at hand to evaluate this influence. The total resistive pressure may be considered to be the sum of the tissue-flow-resistive pressure and the gas-flow-resistive pressure.[93] By measuring the total resistive pressure at a given flow rate for air and for a mixture of gases with the same ratio of density to viscosity, the following expressions may be obtained:

$$\Delta P_{air} = \Delta P_{tissue} + \Delta P_{air\text{-}flow}$$

$$\Delta P_{mixture} = \Delta P_{tissue} + \Delta P_{air\text{-}flow} \times \frac{(\rho \text{ or } \mu \text{ of mixture})}{(\rho \text{ or } \mu \text{ of air})}$$

The tissue-resistance pressure at a given flow rate may be evaluated by solving these two simultaneous equations. By making similar solutions at other flow rates, it is possible to express the pressure-flow relationships of pulmonary tissue resistance.[94]

Figure 4.4-3 presents the averages of results obtained on six normal individuals breathing air and a mixture of ethane and helium with the same ratio of density and viscosity as that of air, but with a change in density and viscosity to 0.75 that of air. It may be seen that the tissue resistance is approximately linear and is roughly 30 to 40 per cent of the total resistance at a flow of one liter per second.

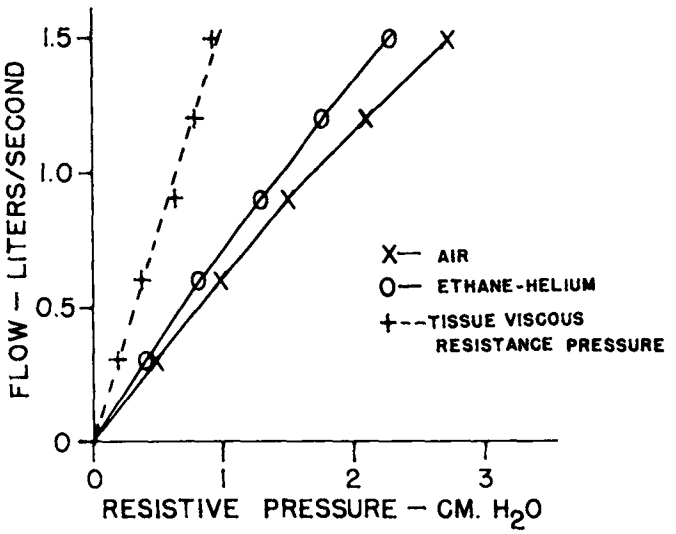

Figure 4.4-3 Mean Flow-Pressure Curves for 6 Subjects Breathing Air and a Helium-Ethane Mixture of Viscosity and Density 0.75 that of Air, along with the Estimated Pulmonary Tissue Resistance Pressures at Various Flow Rates

We may now reconsider the results obtained while breathing helium in the light of the additional information we have at hand as to the tissue resistance of the lungs. Breathing helium is equivalent to breathing air at reduced ambient pressures. As has been stated, the density is approximately one fifth that of air at sea level, while the viscosity is slightly greater than that of air. In Figure 4.4-4 the helium and air data from Figure 4.4-2 are replotted along with the tissue resistance measured in the same subject. It may be seen that the change in resistance associated with breathing helium is even more striking than was at first apparent. The pressure necessary to produce gas flow while breathing helium is represented by the difference between the helium curve and the tissue-resistance curve. The gas-flow resistance has decreased almost in direct proportion to the change in gas density. Actually the best proportionality factor from this experiment and for similar experiments performed on three other normal subjects was 0.8.

If we make so bold as to use this factor in predicting the influence of increases in gas density on pulmonary gas-flow resistance, we can say at 4 atmospheres of pressure, the air-flow resistance should be increased approximately threefold. Because of the presence of tissue-flow resistance was well as gas-flow resistance, the increase in the total flow resistance of the lungs would be less than that for the gas-flow resistance alone. Taking tissue resistance into account, for a fourfold increase in density, the total pulmonary resistance should be approximately doubled.

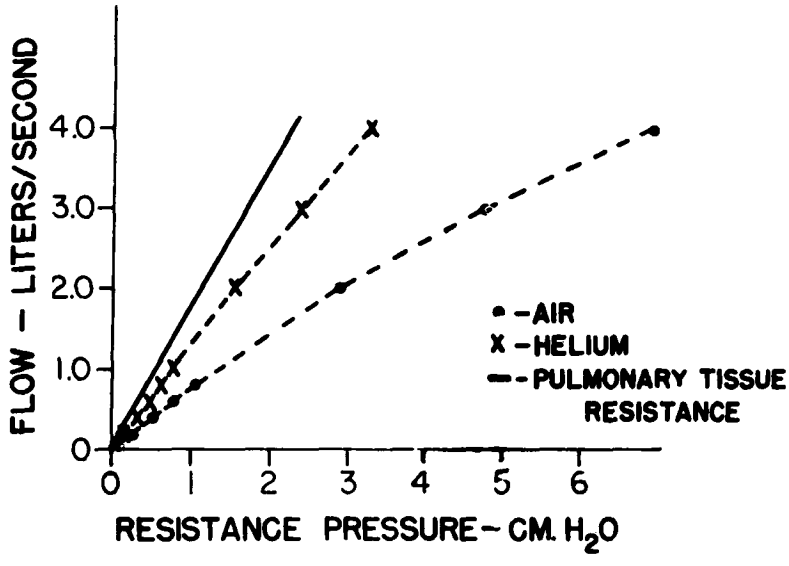

Figure 4.4-4 Helium and Air Flow-Pressure Curves from Figure 4.6-2, along with the Pulmonary Tissue Resistance Flow-Pressure Relationship Measured in the Same Subject

Only a rough approximation has been offered, but fortunately we have some actual data with which to check this approximation. DuBois, Marshall, and Lanphier have recently made measurements of total pulmonary resistance at increased ambient pressures up to 5 atmospheres. They have been kind enough to let me use their data in this presentation. We have had a chance to make one such measurement ourselves. Some of the results of these experiments appear in Figure 4.4-5, where the abcissa indicates the total pulmonary resistance relative to the values obtained at 1 atmosphere, and the ordinate indicates the absolute pressure. The resistances plotted were obtained at a flow rate of one liter per second. You will note that the pulmonary resistance increases proportionately with the absolute pressure, but not in direct proportion. At 4 atmospheres absolute pressure the pulmonary resistance is approximately doubled as was predicted. Approximately the same relationship held for resistances measured at other flow rates than one liter per second.

Up to this point we have neglected the mechanical properties of the respiratory system other than flow-resistance. Since at increased ambient pressures the mass of the flowing gas increases, forces relating to the acceleration of this mass could be expected to change as well. In the single experiment that we performed, it was possible to make an estimate of the pressures relating to volume acceleration as well as to flow-resistance. Figure 4.4-6 shows a plot of pulmonary inertness expressed as the pressure required to produce a volume acceleration of one liter per second per second at various absolute pressures. At accelerations such as would be encountered during extremely heavy exertion, the pressures necessary to produce these accelerations would be only of the order of magnitude of two centimeters of water at ambient pressures of 4 atmospheres. For practical purposes such pressures are negligible. It is of some interest that the inertness appears to extrapolate very closely to zero at zero absolute pressure, which suggests that the tissue inertness of the lungs must be extremely small.

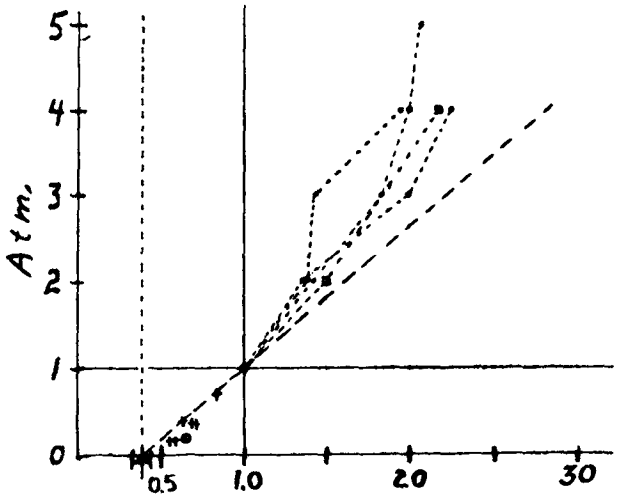

Figure 4.4-5 Total Pulmonary Resistance at a Flow of 1 Liter/Second Relative to that Observed at 1 Atmosphere Plotted against the Absolute Pressure in Atmospheres

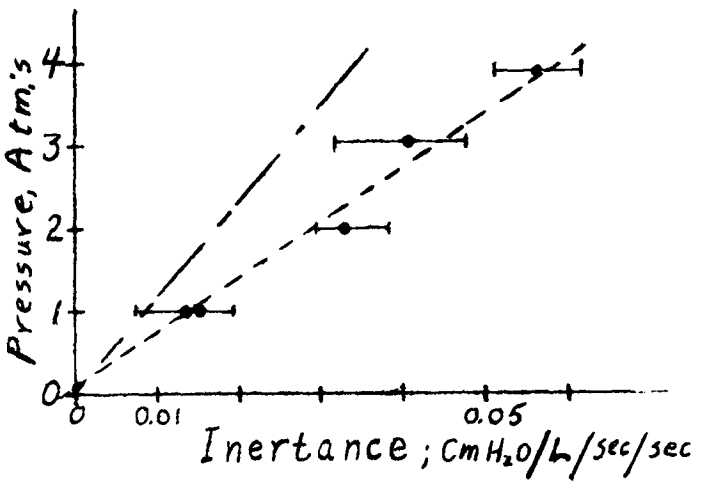

Figure 4.4-6 Inertness of Lungs Plus the Measuring Equipment at Various Ambient Pressures Observed in One Subject

If we are to consider the total flow-resistance encountered during underwater swimming, we must also include the flow-resistance of the equipment being used. In this regard I shall limit my remarks to open-circuit systems. Through the kindness of Mr. Emerson of the J. H. Emerson Company, Cambridge, Massachusetts, I obtained two such units, one Aqua-Lung, and the other the Scott. Figure 4.4-7 represents the flow-pressure data obtained with this equipment. Flows were measured by means of a pneumotachograph. The pressures represent the difference between that measured in the mask or mouthpiece, and the ambient pressure. You will notice that in the inspiratory direction the resistance of the Aqua-Lung, i.e., the pressure required to produce a given flow, was considerably greater than that for the Scott. Approximations of the equipment resistance at various rates of flow and at 1 atmosphere of pressure can be obtained from these plots. The resistance during expiration was approximately the same in the two units.

These measurements were made with the equipment in air. I was curious to find out what happened to the flow-resistance characteristics when the equipment was submerged in water. In particular I wanted to find out what happened to the resistance to expiration. Figure 4.4-8 shows the pressure-flow characteristics of the Aqua-Lung in water. You will note that with the valve five centimeters below the surface of the water, the opening pressure of the expiratory valve was five centimeters, as would be predicted. Considering just the flow-pressure characteristics at pressures in excess of the opening pressure, it may be seen that, if anything, the flow-resistance of the valve is slightly decreased in water.

In making predictions as to what would happen to the resistance of these devices at high pressures, we have one simplifying condition. Demand valve flow is essentially orifice flow. This being the case, for a given pressure difference between the mask and ambient pressure, a fixed mass of gas will be delivered per unit of time. If the ambient pressure is increased fourfold, the mass of gas being delivered by a given demand pressure will be the same per unit of time as that delivered at sea level. The volume of gas per unit of time will be only one quarter that delivered at sea level. Thus, for the same pressure, only one quarter the flow rate observed at sea level would be delivered at 4 atmospheres ambient pressure. From this it may be seen that the inspiratory resistance of such equipment must increase in direct proportion to the ambient pressure.

It is less easy to predict the change in expiratory resistance at increased ambient pressure with such equipment since the expiratory valves do not behave as simple orifices. By extrapolating some information obtained by flowing pure helium through the valves and measuring the associated change in resistance from that of air, an approximation is possible. It would appear that the proportionality factor would be approximately 0.75.

Figure 4.4-9 presents predictions of personal, equipment, and total (personal plus equipment) flow-resistance at various depths. In attempting to predict the changes in personal respiratory resistance, a value for the tissue frictional resistance for the thorax and abdomen, as well as for the lungs themselves, has been included. The addition of further tissue resistance makes a further reduction in the change of total personal resistance with increasing depth. Silverman has found that in individuals working at external work rates of 415 kilo-

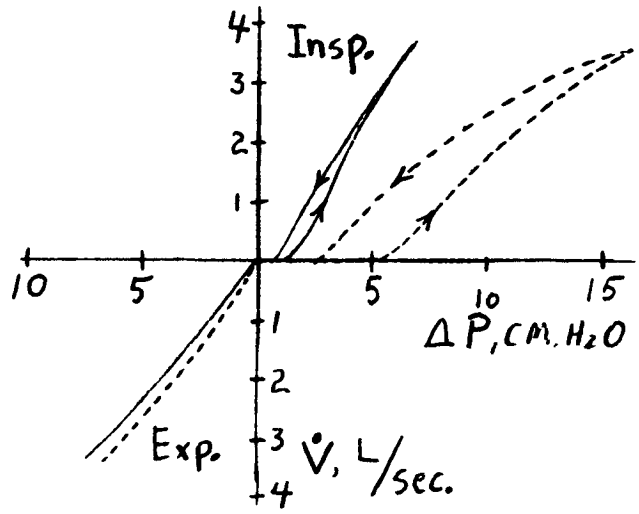

Figure 4.4-7 Flow-Pressure Data Obtained on the Scott Apparatus - Solid Line, and the Aqua-Lung Apparatus - Dashed Line, at 1 Atmosphere Pressure

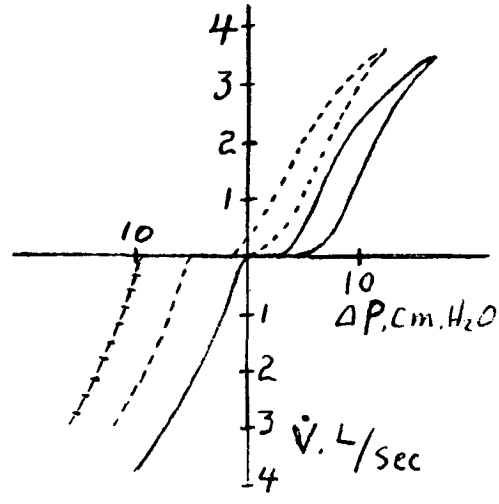

Figure 4.4-8 Aqua-Lung Flow-Pressure Data Obtained with the Apparatus Submerged

grams/minute and with minute ventilation of about 30 liters, flow-resistances equivalent to seven and one-half centimeters of water per liter per second could be tolerated in external breathing equipment without appreciable discomfort. Line A in Figure 4.4-9 was obtained by adding this value to the total personal resistance observed at sea level. It is likely that trained individuals will put up with resistances considerably in excess of this value without complaint. If, however, we take this level of resistance as an optimum, it may be seen that the two pieces of apparatus tested offer resistances far in excess of this level at appreciable depths. In contrast, the personal resistance remains below this level down to depths of 231 feet or 9 atmospheres absolute pressure.

In a sense a happy ending to the problem of resistance to breathing at increased ambient pressures is suggested. It is apparent that the pathology encountered is for the most part man-made and resides in the equipment rather than in the individual. It seems reasonable to hope that inspiratory demand valves can be designed which offer far less resistance to breathing than the ones represented in this report.

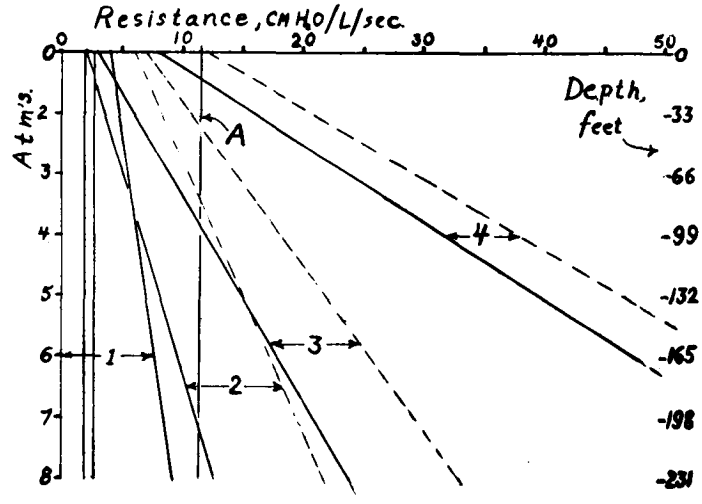

Figure 4.4-9 Estimated Resistance at Depth for Personal Resistance, Expiratory Valves, Scott Apparatus, and the Aqua-Lung Apparatus

COMMENTS

DR. RAHN: I think you have raised many very interesting problems. Some of them are new, and we have another team that might be able to make some comments.

DR. LANPHIER: This has been a remarkable analysis of the situation. We have a tremendous amount of data on this subject, and what has just been presented seems to agree very well with it. The big problem still remains -- just how much can a man stand. The values in that respect, although we never have been able to do a good study on the subject, seem to be quite a bit higher than would be predicted on a theoretical basis from work such as that of Silverman. The men really put up with a lot before they complained loudly. This whole thing could be a subject of a couple of days' conference at least.

DR. BURTON: I should like to congratulate Dr. Mead on a beautiful piece of biophysics because that is what it is and ask him whether the matter of turbulent and laminar flow through the system could be investigated directly. Do we have rapid sounding techniques which are good enough so that we could support a catheter in the esophagus of an animal at five different places, the middle and side, et cetera, and get these flow curves in one expiration? It would be interesting to see how much sooner the gas in the center of the trachea traversed a given distance than further toward the periphery. Do you think there is a direct approach to this experimentally?

DR. MEAD: Dr. Burton, I have thought some about that and have wondered about the possibility of constructing a transparent model, perhaps a cast of the upper part of the respiratory tree. As for the actual measurements, I have no notion of how rapidly they might be accomplished. The fastest equipment might possibly be Dr. Forester's mass spectrograph, but I do not know. It would be technically a tremendous problem in the tube experiments, but in animal experiments it would not.

DR. LAMBERTSEN: You mentioned, Dr. Mead, the problem of volume inertness, the point you raised about setting gas in motion at high pressure. There is a displacement of water by the chest when the individual is immersed in water. The sea becomes part of his chest wall, and he has to move the whole ocean when he expands his chest. Can you comment on that?

DR. MEAD: Yes. I thought about it and I do not know how to handle this readily. I thought if I get a chance, I will go over and try some things in the pool to see what happens to my maximum breathing capacity immersed as compared to out. I never did it. I just had the intuitive notion that the forces would be small, but I am probably wrong about it.

DR. LAMBERTSEN: I think your intuition was correct. The effects, subjectively, are not very great, but I have always been surprised that they were not. I wondered perhaps whether by increasing the frequency of respiration in the water, you might not encounter a sharp increase in the inertness effect on the chest wall.

DR. MEAD: There would be flow as well as inertia.

DR. PAPPENHEIMER: I noticed that from your data the respiratory frequency is likely to be extremely low in this work. I wonder if this is a matter of people being taught to breathe this way or if this is a natural phenomenon that people normally breathe very slowly while submerged in order to prevent the build-up of pressure.

DR. RAHN: Dr. Schaefer, I am sure you have a comment on that.

DR. SCHAEFER: We can observe that people who are trying to use this apparatus or trying to dive have low respiratory frequency and high amplitude.

DR. LAMBERTSEN: Part of that seems to be training, I believe, but there is also the possibility that the high inspiratory resistance contributes to a slow respiratory rate.

DR. RAHN: That should be easily visible from the pneumogram records. I wanted to ask both authors whether they observed a change in pattern of the respiratory frequencies?

DR. MEAD: In our case Radford was told to breathe at a certain rate and at a certain depth. It seems to me we ought to have Dr. Otis comment here because he measured changes in respiration during breathing through high resistance at rest and discussed other work in a paper some years ago. It is also apparent in Silverman's data that there seems to be a substantial reduction in frequency with increased resistance.

DR. RAHN: I think one would also expect to get a flatter pattern.

DR. MEAD: Yes, you do, definitely. The optimum pattern in a resistance system of that sort ought to be square waved.

DR. BEHNKE: Dr. Lambertsen, did you say one was breathing against the resistance of the ocean under water? I did not quite follow that.

DR. LAMBERTSEN: The point I was raising is as you inhale, you actually must displace or move a mass of water. Entirely apart from any pressure effect is an inertial effect of taking a bit of water and moving it from this place to a different place in the ocean.

DR. BEHNKE: On the matter of resistance I think apart from the excellent analysis which was commented on by Dr. Burton, the gist of what you had to say was that breathing resistance was proportional to the square root of the density approximately, that is, at 4 atmospheres the resistance was doubled. What value would one get from helium-oxygen mixtures compared with air?

DR. MEAD: Arthur DuBois has some experimental information on that.

DR. DUBOIS: Dr. Lanphier has an exhibit at the Diving Unit which will have the data on diving at 133 feet simulated depth, with the subject breathing

helium at normal and maximum flow rates, and the result is that the helium makes the resistance less, so that it is equivalent to approximately 60 feet of depth instead of 133 feet. In other words, you get a marked improvement with helium on these mechanical resistance factors.

DR. BEHNKE: Was density the predominant factor as one would predict on theoretical grounds or does viscosity appreciably alter it?

DR. DUBOIS: When you get to high flow rates such as you might expect with a person working, it seems the density is the major factor and the other one almost drops out.

DR. MEAD: I do not think you can talk about density and viscosity in those terms. You have to consider the ratio of those two since this influences the distribution of turbulence. It is very hard to attribute so much to viscosity and so much to density. After all, the underwater swimming problem is a density problem in terms of what happens to the air. It would appear that there is no practical way of reducing the viscosity of any gas mixture you might want to make, so it is not a practical point. The individual resistance is not a big thing itself. This is not a big thing that you have to do a great deal about at almost any reasonable depth.

DR. DUBOIS: Except possibly under maximum working conditions, then it might.

DR. MEAD: I doubt even then that it would be. There is so much more to be done on the equipment than there is on the individual at this point.

DR. MENARD: I wonder how that Aqua-Lung is adjusted. I would hate to learn the device is impractical without being sure that it was being used to its best advantage.

DR. MEAD: After all, I borrowed this Aqua-Lung and hooked it up the best I could and puffed on it to get it going as easily as I could. I am using it as an example merely to show that the resistance of such a device should be proportional to the density of the gas. That is why I did not put the names on the slides and should not have mentioned them in the talk.

DR. MENARD: We used to get very serious coughs and begin to run low fevers after a couple of hours using an Aqua-Lung until we got it adjusted. Now we do not have that difficulty. Now we have the flow as fast as it will come.

DR. LANPHIER: There is a definite difference between the flow characteristics of these two types of apparatus and the problem of breathing resistance in diving has not been studied thoroughly enough to permit saying which is better. For example, the Aqua-Lung may have higher breathing resistance than the other, even during ordinary activity, and the resistance increases considerably as greater flows are demanded. But with effort it can be made to deliver rather tremendous flows.

In the other apparatus even full opening of the demand valve requires relatively little negative pressure. However, there is a definite point of maximum flow. Beyond this the flow increases very little regardless of the 'suction' applied. We are not completely certain that the present maximum flow of this apparatus is adequate for all contingencies. We believe it is, but this illustrates another aspect of apparatus evaluation which must be considered and which requires further study.

4.5 INERT GAS NARCOSIS

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Despite their chemically unreactive nature, the noble gases at certain pressures display all the typical properties of anesthetic agents. It is of special interest that these inert, nonbonding substances are capable of the same alterations of nervous activity which more reactive narcotic and depressant substances exert, for example, the alcohols and the barbiturate derivities. The over-all anesthetic effect of inert and unreactive gases may be appreciated by a glance at the first table, Table 4.5-1, where the isonarcotic pressures of a group of inert and unreactive gases are listed. At these partial pressures, there is an equivalent depression of central nervous system activity. In this case an equal protection is afforded to a group of mice from the effects of an applied electroshock current. Those gases above nitrous oxide on this scale may, of course, be used as general anesthetic agents to induce unconsciousness. These figures are only relative anesthetic partial pressures and are intended for comparison with one another. For example, since surgical anesthesia is accomplished in patients breathing 80 per cent of an atmosphere of either nitrous oxide or xenon, (96) one may predict from their ratio with nitrogen that the same degree of nitrogen anesthesia would result in a diver breathing air at 38 atmospheres (1200 feet). This agrees with experiments performed upon several types of laboratory animals where a partial pressure of nitrogen greater than 30 atmospheres was required to abolish the righting reactions.

GAS	ED50 Atm.	Conc. in 'lipid phase' (olive oil) at Isonarcotic partial pressure mM/L
Cyclopropane	0.045	.036
Dichlorodifluoromethane	0.26	.057
Ethylene	0.47	.026
Xenon(96)	0.51	.038
Nitrous Oxide	0.58	.036
Krypton(96)	1.8	.034
Sulphur Hexafluoride	1.87	.020
Methane	2.9	.043
Argon	12.6	.077
Nitrogen	18.0	.052
Helium	163.0	.107

Table 4.5-1 Oil Solubility of Various Inert and Unreactive Gases at the Isonarcotic Pressure

According to Costeau[97] the onset of euphoria and defective judgment usually occurs in Aqua-Lung swimmers at 6 atmospheres air pressure (200 feet), which in terms of nitrogen concentration is only one sixth of the amount required for anesthesia. Divers breathing helium-oxygen mixtures, which have considerably less anesthetic action than nitrogen, could possibly descend to a depth of 1500 feet without mental aberrations, provided the attending hydrostatic pressure of 45 atmospheres was of no consequence.

At their isonarcotic partial pressure or concentrations, all the gases are in good agreement with the Meyer-Overton hypothesis[98] (Figure 4.5-1, left). This time-honored theory postulates that any inert substance will exert a depressant action on the nervous system when a sufficient quantity becomes dissolved in its lipid phase. Therefore, the physical property of a solubility measured in this case in olive oil determines the relative potency of a particular agent. The partial molal-free energy, another physical property of gas molecules, has been suggested by Ferguson[99] and by Brink and Posternak[100] as a useful anesthetic index and is derived from the ideal vapor pressure of the substance or the fugacity (Figure 4.5-1, right). This value defines the tendency of a molecule to enter a phase and remain there as long as steady-state conditions prevail. This is almost the same statement as the Meyer-Overton theory except the gas solubility can be predicted in accordance with Raoult's law from the fugacity, and it is independent of the phase in which it is dissolved. Inherent in both concepts of narcotic action is the facility with which a gas molecule occupies a nonaqueous phase in attaining a critical concentration. This may determine the relative potency of anesthetic agents, but it will not explain the mechanics of their production of the narcotic state.

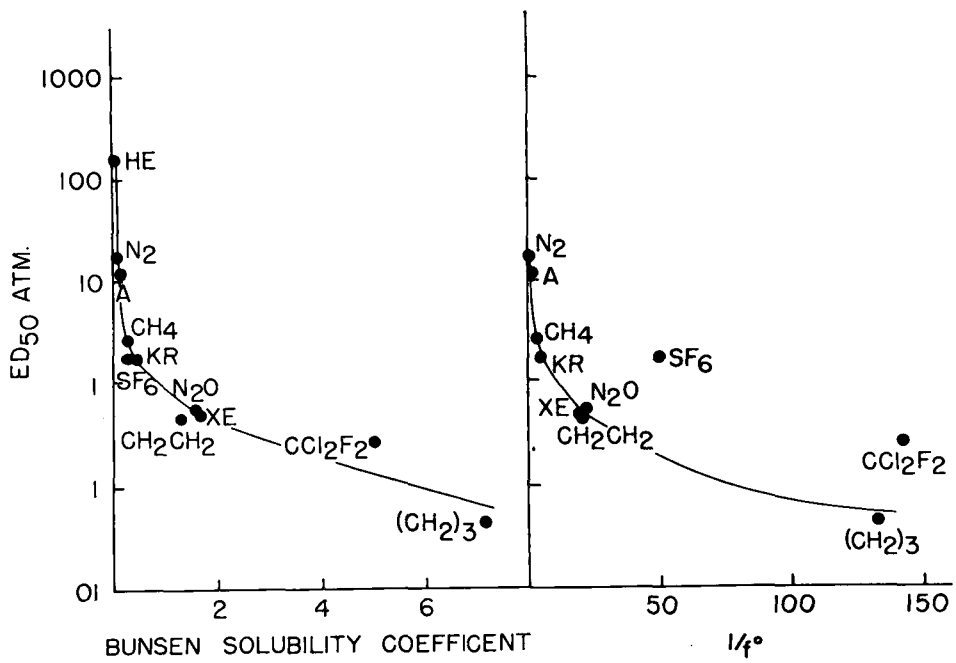

Figure 4.5-1 A Comparison of the Isonarcotic Pressure of Various Gases on the Basis of Bunsen Coefficients and Fugacity

The most likely site of action of central depressants is at certain synaptic pathways in the higher centers of the nervous system[101] which are extremely difficult to study by existing chemical methods during the onset of narcosis. On the other hand, if transmission in the synapse is at least partially related to the process of fiber conduction in an isolated nerve, a study of the alteration of this function by narcotics might prove illuminating. The nerve axon has been extensively studied and considerable information is available about this structure.[102, 103]

As might be expected, a higher concentration of a particular agent is required to suppress excitation and conduction in nerve fibers or axons than to suppress transmission in central nervous system synapses. This relation can indeed be seen in Figure 4.5-2, where the gas pressures required for both processes are plotted against their tendency to partition or dissolve in a nonaqueous phase. While the quantity required for blockade was always much greater than the amount necessary for central nervous system depression, the fact that the ratio between the two is fairly constant over a wide range of gas concentrations suggests that the two systems are affected in a very similar fashion.

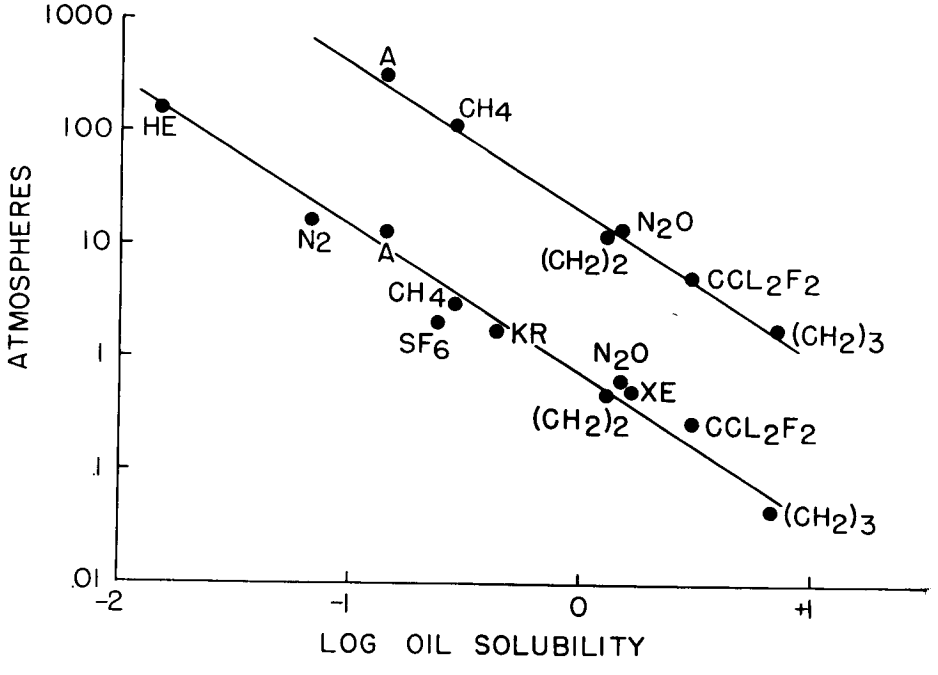

Figure 4.5-2 Relation of ED50 Pressures to the Pressures Required for Reversible Nerve Fiber Blockade in the Rat Sciatic Nerve

Of the theories of anesthesia that have been proposed only the so-called metabolic theory advanced by Quastel offers an explanation of the actual mechanics of its production.[104] In the narcotic state the rate of carbohydrate oxidation of the brain is said to be diminished due to enzymatic inhibition produced by the presence of the narcotic agent. It is well known that energy derived from the oxidation of substrates is essential for the proper functioning of cells, and this is especially true when applied to transmission of impulses in synapses[105] and axons.[106] However, one of the main objections to this concept of metabolic alteration by narcotics is the rather large difference between in vivo anesthetic concentrations and in vitro concentrations required to inhibit substrate oxidation.[107] Although metabolic inhibition of various tissue substrate preparations has been repeatedly demonstrated by the use of agents like the barbitals and alcohols,[108, 109] any attempt to show a similar action for the anesthetic gases has been unrewarding when carried out with conventional Warburg techniques at less than 1 atmosphere partial pressure.[110] It is rather important in this connection that the concentrations of barbiturates and alcohols which produce a measurable depression of the oxidation of a substrate like pyruvate by homogenates of nervous tissue is identical with, or less than, the concentration which blocks the transmission of impulses in isolated nerve (Table 4.5-2).

Minimum Con. for:	Blockade	30-50% Inhib.
Phenobarbital	10-15 mM	5.0 mM
Chloretone	5-7	3
Urethane	200	25

Table 4.5-2 Comparison of Concentrations Required to Produce Measurable Reduction in the Rate of Oxidation of a Substrate by Nerve Tissue Homogenates and to Block Transmission in Isolated Nerves

In our laboratory experiments were conducted which enabled us to determine the disappearance rate of a Krebs-cycle intermediate, namely, pyruvate, under gas pressures much greater than atmospheric. A first-order reaction describes this system, that is, the rate of disappearance is proportional to the logarithm of the substrate concentration, which in our experiments ranged between 1.0 and 3.0 millimoles per liter (Figure 4.5-3). Pyruvate, added to homogenates of brain and nerve, is oxidized to carbon dioxide and water by a series of enzyme complexes often referred to as the cyclophorase system.[111]

The rate of this reaction is diminished by some 30 to 50 per cent by the addition of 2.0 to 3.0 millimoles per liter of chloretone or phenobarbital, a finding which agrees with observations reported by others. As previously mentioned, these concentrations are the same or are somewhat smaller than those which block the conduction of impulses in isolated nerve fibers. However, the minimum gas pressure which produces blockade of nerve conduction does not measurably inhibit disappearance of pyruvate. Indeed, with the two gases employed (nitrous oxide and cyclopropane), no change in energy release in our in vitro system was observed until the partial pressure in equilibrium with the substrate homogenate was twice this amount. The specific step where the conversion of pyruvate is diminished by

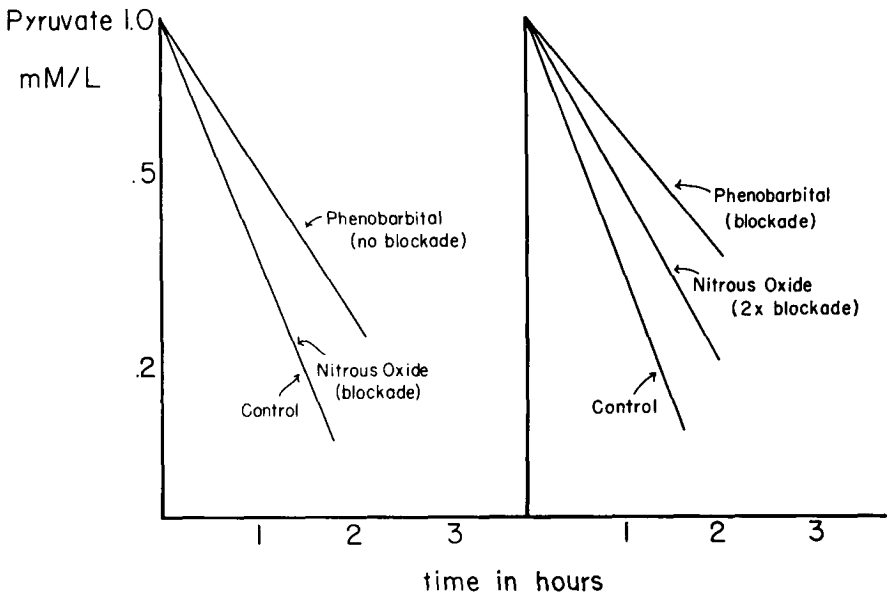

Figure 4.5-3 Pyruvate Disappearance in Rat Brain Homogenates

agents of this kind remains unknown, but is believed not to involve a dehydrogenase.[101] It appears that the oxygen consumption of nerve fibers[102] or their Krebs-cycle metabolism may be depressed without inducing conduction blockade; yet when blockade supervenes upon further addition of a blocking agent, these energy sources are greatly diminished. If there is a direct cause-effect relationship, that is, if blockade is the result of reducing the available energy obtained from the oxidation of carbohydrate fragments, it is possible to state that the gases create conditions unfavorable for impulse conduction by an unrelated mechanism.

Recent studies by Abood, Gerard, and associates[112, 113] have shown that the oxidation of many Krebs-cycle intermediates, including pyruvate, occurs almost exclusively in the mitochondrial fraction of nervous tissue homogenates. About 50 per cent of the total phospholipid content of the central nervous system can be accounted for by these microscopic structures.

In view of the active role of mitochondria in high energy exchange and oxidative phosphorylation, it would be tempting to say that the mitochondria represent the "lipid phase" proposed by H. H. Meyer. It remains to be seen, however, whether the highly polar phospholipids present in these particles would behave toward inert and unreactive gases in the same manner as olive oil or benzene.

DR. BURTON: I should certainly like to ask about the interesting graph of solubility against the partial pressure of the gas required for an anesthetic effect. It seems to me that you said this graph fitted in with an idea that for a given anesthetic effect, the same number of molecules dissolved per liter was required, whatever the species of molecule. When I did a little mental arithmetic, it seemed to me that the graph said the opposite. It seemed that in the case of argon and nitrogen far less molecules were effective.

DR. CARPENTER: The concentration or numbers of molecules per unit volume dissolved in the lipid phase at the isonarcotic concentrations of the gases appear to be fairly uniform. Now with helium and sulphur hexafluoride you might speculate that their very small or very large molecular size, respectively, was a contributing factor responsible for their deviation.

DR. RAHN: May I ask this question, Dr. Carpenter? Do you mean to say that the concentrations available per unit volume represented on that curve are all identical?

DR. BURTON: I am afraid I am being stupid about this, but the graph looked so far from a hyperbola.

DR. RAHN: I had the same reservation. I wondered if you misspoke, or simply wanted to say there was a relationship, or that it obeyed exactly the Meyer-Overton law.

DR. CARPENTER: Yes, it obeys exactly the Meyer-Overton hypothesis, that is, at the isonarcotic pressure the concentrations of the gases in a lipid phase like olive oil are very similar. I think it is well to point out that if you considered all the gases from the ED50 of cyclopropane to the ED50 of helium, there is a one-to-four thousandfold difference in the inspired gas pressure. Yet when you consider it from the standpoint of the partial pressures of each gas, times its measured olive-oil solubility at 1 atmosphere, you find only a four-to-fivefold difference. Again when you solve for the same thing employing instead the solubility of the gas in a nonpolar liquid like benzene, it turns out to be an equally good correlation. If we omit helium and sulphur hexafluoride, there is just a threefold difference in concentration over the entire range. To be sure, with nitrogen a little lower moles-per-liter concentration exists in the lipid phase compared to argon. This might be rectified by a more precise measurement of their solubility. Helium, on the other hand, being a very insoluble gas, we don't really know whether the actual measurements that have been given in the handbook are entirely accurate. Does that answer your question?

DR. BEHNKE: Don't you know what the solubility of helium is in olive oil?

DR. CARPENTER: Well, it is very hard to measure the solubility of any gas in olive oil because it is so viscous. I found it took me the better part of the day with almost continuous shaking to equilibrate it, yet in benzene, which is of course less viscous, mixing occurs quickly, and you can determine the solubility

in benzene much more rapidly, in twenty or thirty minutes with continuous shaking. With olive oil it was impossible to believe you had complete equilibration until you had done the determination the better part of the day, and due to the leaks in the system that might occur, I always had reservations concerning the published figures for olive oil solubility. In a comparative study Lawrence, I believe, has shown there are quite a few different gas solubility values given for olive oil. For benzene, however, there is rather good agreement in the literature.

DR. BEHNKE: In the Meyer-Overton hypothesis is it not the oil-water ratio that is important?

DR. CARPENTER: What I am talking about is gas-oil phase. I think what you are bringing up is an oil-water, or gas-water-oil phase system. After equilibrium it would amount to the same thing from the standpoint of numbers of molecules in the oil phase. The fact that you can't use water solubility alone is, I think, apparent because water is so highly polar and gases do not behave ideally in water. They do behave ideally -- I think it is an accident -- in olive oil. I believe they behave better in benzene or carbon tetrachloride, which are both nonpolar.

DR. HAUGAARD: I want to ask whether your blockade effects have been found to be reversible?

DR. CARPENTER: Yes, they are.

DR. RAHN: I found it rather exciting to extrapolate Dr. Carpenter's curve to the other extreme. If we could get enough radon gas, I would suggest that radon would be a very good anesthetic agent in the operating room because it would only require one-tenth of one per cent to anesthetize us.

4.6 THE ROLE OF CARBON DIOXIDE IN THE PHYSIOLOGY OF HUMAN DIVING

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In this paper I shall speak about the role of carbon dioxide in skin diving. I should like to discuss the results of two series of investigations; first, respiratory metabolism changes during diving, and second, adaptation to diving in instructors at the Escape Training Tank in New London.

The Escape Training Tank gave us the unique opportunity to study the alveolar carbon dioxide and oxygen tensions as well as the metabolism before, during, and after diving up to 90 feet. A modified Haldane technique was used to sample the alveolar air. The subject exhaled most of the air into a large rubber bag, closed the clamp, and exhaled the rest of the air into a small bag (Figure 4.6-1). After exhaling the air into the bags at 90 feet, the subject stepped into a bell and took a deep breath. The samples at 90 feet were collected over mercury in Bailey bottles. The duration of the dives to 90 feet amounted to 1-1/2 to 2 minutes. Alveolar carbon dioxide and oxygen tensions during and after dives to 90 feet were compared with those obtained after breath holding at the surface. Dive and breath holding times were kept at approximately equal lengths of 1-1/2 to 2 minutes.[114]

Figure 4.6-2 shows the alveolar pathway during dives to 90 feet and during three minutes of breath holding using the pO_2-pCO_2 diagram.[115] The resting alveolar carbon dioxide tension is 38 to 40 mm Hg and that of oxygen about 150 mm Hg. At the end of a deep inhalation oxygen tension increases to 125 mm Hg and carbon dioxide tension drops to 25 mm Hg. During breath holding the alveolar carbon dioxide tension increases to about 50 mm Hg and oxygen decreases to about 60 to 70 mm Hg. The shaded areas indicate standard deviations. At the end of the descent to 90 feet, oxygen tension rises to about 200 mm Hg and carbon dioxide tension does not increase above 43 mm Hg. At the end of a round trip, descent to 90 feet and ascent to the surface, the alveolar oxygen tension reaches extremely low values, 25 to 35 mm Hg, while the carbon dioxide tensions do not increase correspondingly. We should have had values where the question mark is indicated. What happened to the carbon dioxide?

In a second series of experiments in which the alveolar carbon dioxide prior to and after the dive was continuously recorded with an infrared carbon dioxide analyzer, it was found that after the dive the alveolar carbon dioxide tension was elevated considerably longer than after breath holding of equal length in the same subjects. As shown in Figure 4.6-3, the alveolar carbon dioxide tension is higher immediately after breath holding, but drops within one minute to practically normal levels, while the alveolar carbon dioxide tension after diving remains elevated for four minutes. This indicates a delayed carbon dioxide excretion after diving.

Figure 4.6-4 shows measurements of blood gases, lactic acid, respiration, and metabolism in one subject before and after a dive to 90 feet. The carbon dioxide content of the blood rose only very slightly, while the oxygen content dropped

RECORDING PULSE RATE UNDER WATER

ALVEOLAR AIR SAMPLING UNDER WATER

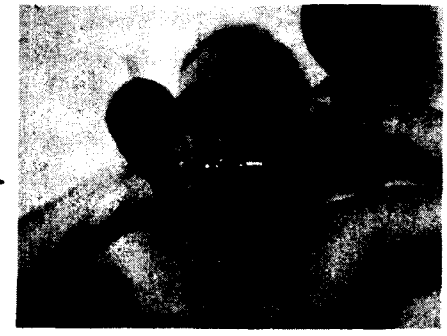

Figure 4.6-1 Alveolar Air Sampling and Recording Pulse Rate Under Water

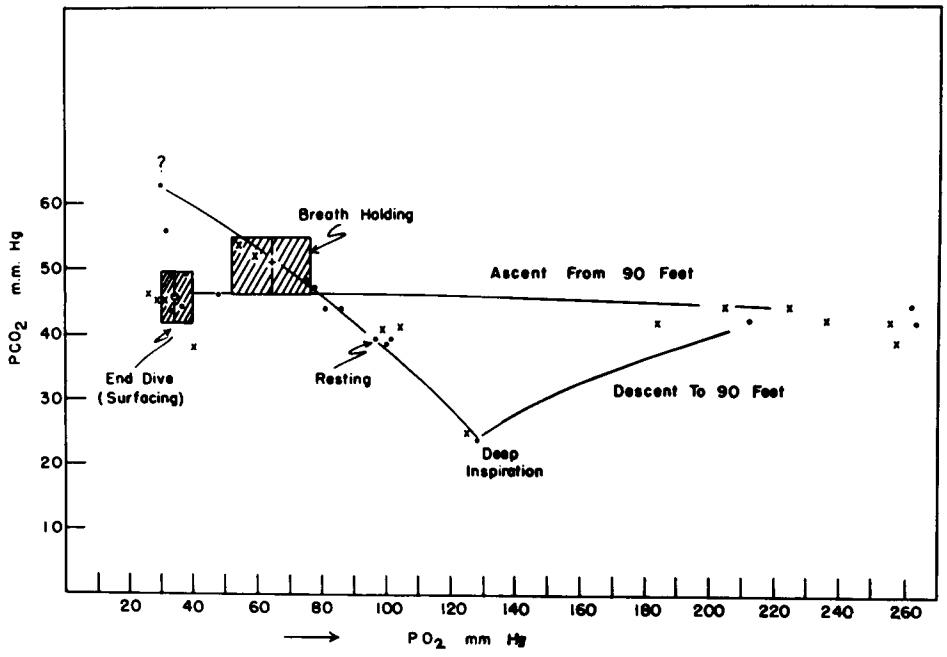

Figure 4.6-2 Alveolar Pathways during Breath Holding at the Surface and Dives to 90 Feet of Approximately Equal Duration (1.4-2 minutes)

during the dive. The lactic acid content in the blood rose from 9 mg per cent to 55 immediately after the dive and fell to 25 mg per cent within five minutes after the dive. Respiration was increased threefold during the first minute after the dive and returned to normal level within 15 minutes, showing a second rise during the period between 6 and 12 minutes. The excess oxygen uptake above the control level after the dive was limited to 4 minutes and amounted to 1400 cc. We have found corresponding values in three other subjects. This would indicate that the oxygen debt taken during the dive of approximately 1-1/2 minutes is in the order of 1400 cc. The excess carbon dioxide exhalation within the first 4 minutes after diving amounts to 900 cc in this case. In the whole series of experiments carried out on more than ten subjects, we never found a respiratory quotient above one during the first 5 minutes after the dive. Also, one would expect from the large rise in the lactic acid content of the blood that carbon dioxide would be forced out of the blood, thereby increasing the respiratory quotient. However, it was observed that for short periods during the later recovery period between 5 and 10 minutes, the respiratory quotient rose above one.

In four experiments in which arterial and venous blood samples were drawn prior to the experiment, immediately after the dive, and 3 and 6 minutes later, it was found that the plasma carbon dioxide content either did not change or was only

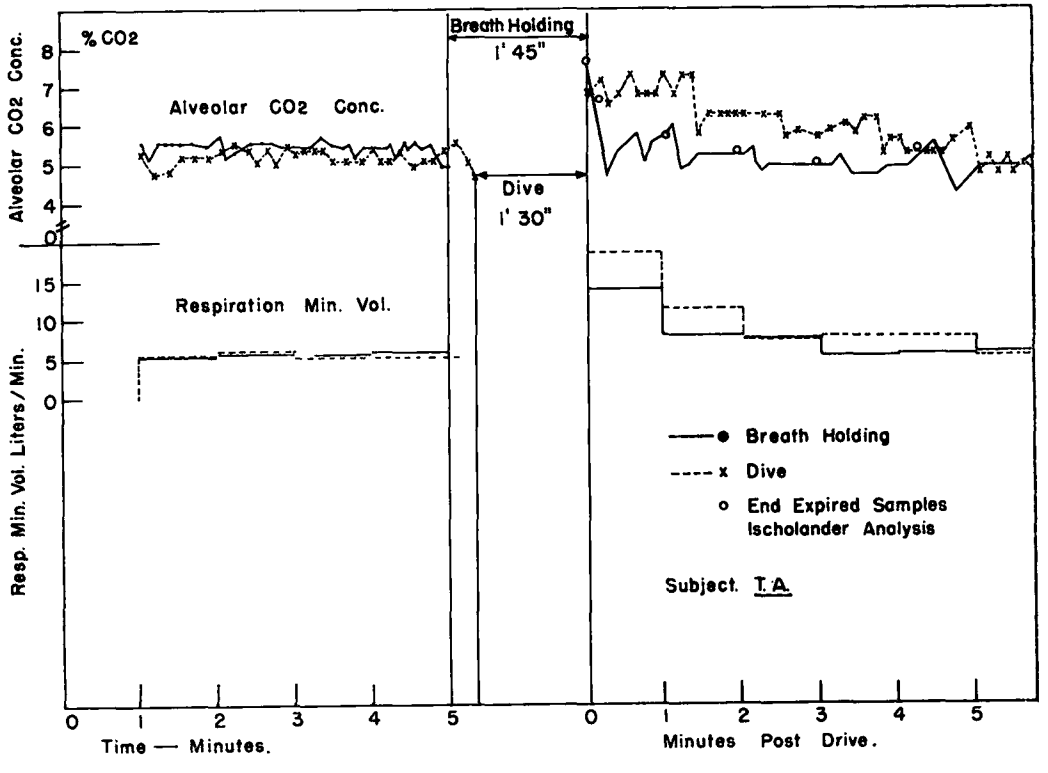

Figure 4.6-3 Alveolar CO_2 and Respiratory Minute Volume Prior to and After Breath Holding at the Surface and Dive to 90 Feet

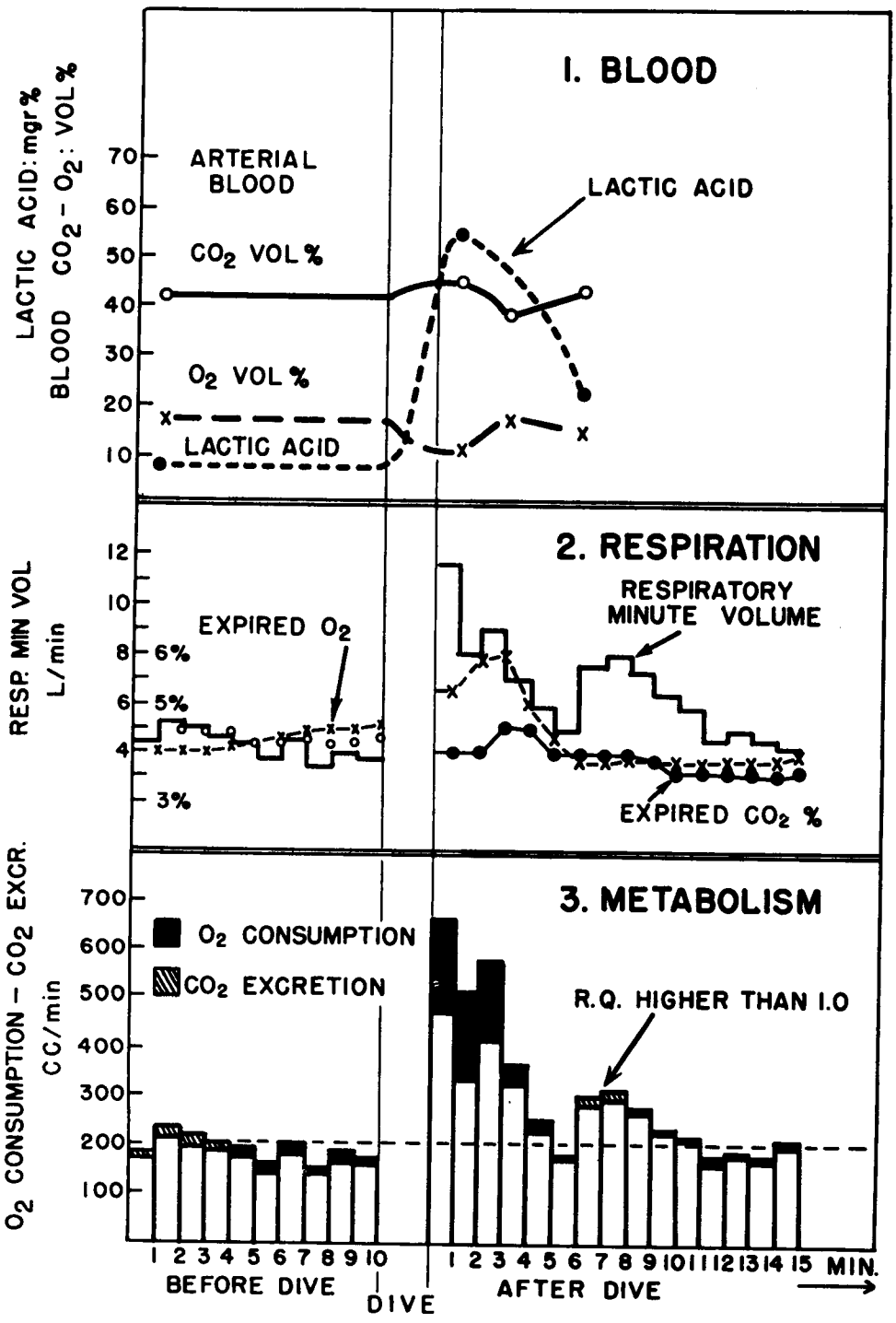

Figure 4.6-4 Measurements of Blood Gases, Lactic Acid, Respiration, and Metabolism in One Subject Before and After a Dive to 90 Feet

slightly elevated, while the carbon dioxide content of the cells as well as the water content of the cells was reduced immediately after the dive. These findings suggest a possible interference with carbon dioxide transport from plasma to the cells.

SILENT BUBBLE FORMATION

The two important findings of these studies were (a) the delayed carbon dioxide excretion, and (b) the increased nitrogen content of the alveolar air at the end of the dive (89 per cent compared with the normal 79 per cent). These findings can be explained by the difference in rate of elimination of nitrogen from that of carbon dioxide. Nitrogen and carbon dioxide as well as oxygen gas tensions in the lungs are increased threefold at a depth of 99 feet. Under these circumstances nitrogen as well as carbon dioxide and oxygen diffuse from the lungs into the blood. Nitrogen follows the law of solubility of gases in liquids in relation to partial pressure. In carbon dioxide uptake of the blood three factors play a role: solubility in liquids, chemical combination with alkali buffer, and carbon dioxide transfer between plasma and cell system. The reservoir to take up carbon dioxide appears much larger than that for nitrogen. During descent, which represents a form of rapid decompression, nitrogen is rapidly released from a small store under high pressure, while it takes longer to release carbon dioxide from a large store.

In the four experiments mentioned, in which arterial and venous samples were drawn, it was observed that the first 2 cc of arterial and venous blood drawn after a dive had a foamy appearance; with the following 1 cc or 2 cc of blood the foam disappeared. Since neither the alveolar carbon dioxide tensions of samples collected within five seconds after surfacing, nor the blood carbon dioxide tension of samples obtained during the first 30 to 40 seconds showed a large increase, it is concluded that the foam of the first 2 cc of blood consists of nitrogen. The foam disappeared approximately 10 seconds after surfacing, or 40 seconds after starting ascent. This is apparently at the end of the second circulation time.

It is interesting to note the conditions under which "silent" bubble formation not leading to symptoms of decompression sickness occurs; a decompression ratio of 3:1; a rate of ascent of 3 feet per second; work during ascent, and climbing up a line.

Interpretation of our findings as silent bubbles is in line with the view expressed by Bateman[116] that the decompression ratio at which bubbles tend to grow may be far below the symptom threshold. Behnke, Feen, and Willman[117] expressed a similar opinion that bubbles form as soon as a state of supersaturation is initiated. On the basis of results obtained in these studies, some comments can be offered on the theory of bubble formation. According to Whitaker[118] and Harris,[119] carbon dioxide has a primary role in the development of bubbles which, under conditions of altitude decompression and muscular activity, consist at first mainly of carbon dioxide, which is later replaced by nitrogen. Results of our experiments with decompression following a short high-pressure exposure and involving muscular work seem to indicate that bubbles are primarily formed from nitrogen, but that carbon dioxide may possibly influence bubble formation indirectly through the interference of the carbon dioxide transport from plasma to cells.

Bubble formation during decompression from depth and decompression to altitude might differ in several respects. Behnke[120] pointed out that the altitude bubbles have a greater water and carbon dioxide content.

ADAPTATION TO DIVING

It is quite evident that skin diving produces a considerable stress on the diver. The question, of course, came up as to whether adaptation to this condition takes place. We tested various physiological functions of those tank instructors who really are able to dive to 90 feet and compared the results with those obtained from randomly selected laboratory personnel.

THE BREATH HOLDING TIME

The breath holding time of tank instructors was measured and found to be 105 seconds, while that of a group of laboratory personnel was 60 seconds. The vital capacity of 16 tank instructors was compared with the vital capacity of 16 laboratory personnel. It was found that the vital capacity of the tank instructors was not only significantly larger than that of the group of laboratory personnel, but it was also 20 per cent higher than could be predicted on their height, weight, and age, using the West formula.[121] Figure 4.6-5 shows a comparison of the total lung volumes of the tank instructors and the group of laboratory personnel. It can be seen that the tidal volume, the respiratory reserve, vital capacity and total capacity measure is larger in the tank-instructor group. To decide whether the lung volumes really change during the course of duty at the tank, a longitudinal study was carried out and the lung volumes of tank instructors measured at the beginning of their tour of duty and after one year. Inspiratory reserve, tidal volume, vital capacity, and total capacity showed a significant increase, while residual capacity showed a trend to decline, Figure 4.6-6. Since the depth a man can reach depends upon the ratio of residual capacity to total lung volume, an increase in the total lung capacity and a decrease of the residual capacity increases the depth the diver can reach. This could be considered as one form of physical adaptation to diving. Since the breath holding breaking point is determined by carbon dioxide and oxygen tension, we were interested to know whether sensitivity to carbon dioxide and to low oxygen is lower in these tank instructors.

Figure 4.6-7 shows the ventilatory response as a function of alveolar pCO_2 in two groups of subjects, laboratory personnel and tank instructors. Alveolar ventilation in liters per minute was computed from the observed total minute ventilation, frequency, and estimated dead space for each of the 10- to 15-minute periods of exposure to the various concentrations of carbon dioxide. The combined physiological and mask dead space was estimated to be 220 cc. The mean values of the alveolar ventilation under various carbon dioxide concentrations were plotted as multiples of the alveolar ventilation under air (ventilation ratio = 1 under air). It can be seen that normally, while breathing air, the tank instructors have a higher alveolar carbon dioxide tension.

The stimulus response curves of the tank instructors differ from those of the laboratory personnel in (1) the intercept with the O line, and (2) a flatter slope. This indicates that in the tank instructors the threshold of alveolar carbon dioxide to produce a detectable response is higher, and the sensitivity to carbon dioxide is lower than in the other group. (Ventilatory response to 5 per cent and 7 per cent carbon dioxide is statistically significantly different, $P = 0.001$.)[122]

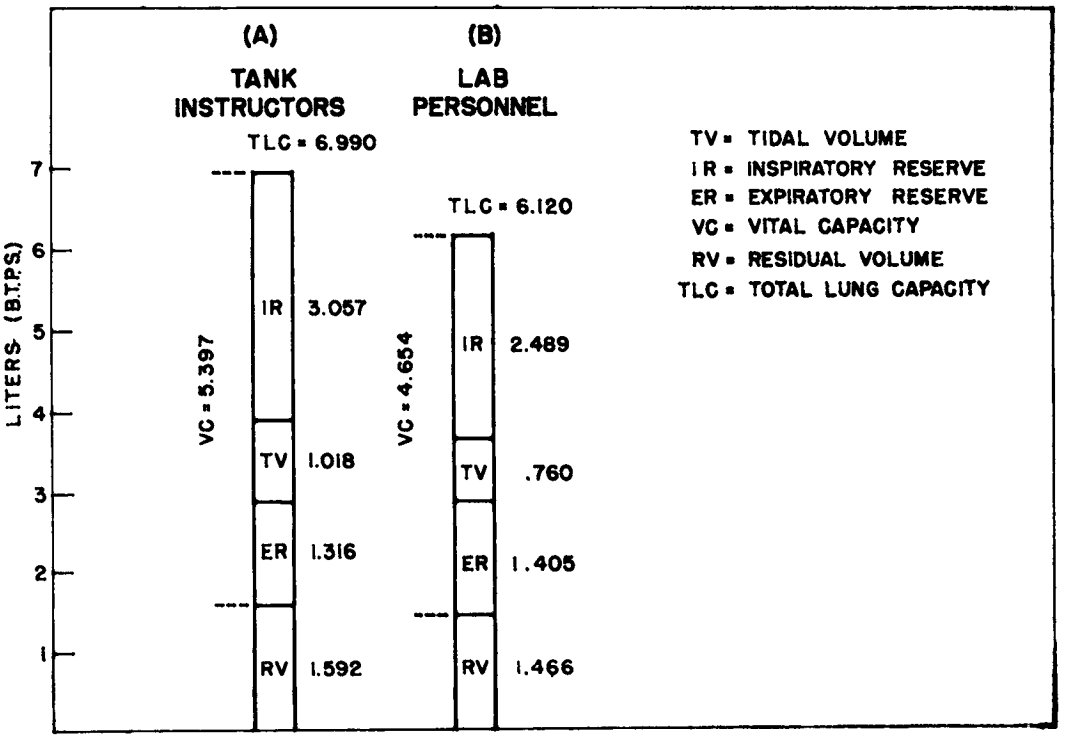

Figure 4.6-5 Mean Values of Pulmonary Capacity and Its Subdivisions from a Group of 16 Laboratory Personnel and a Group of 16 Tank Instructors

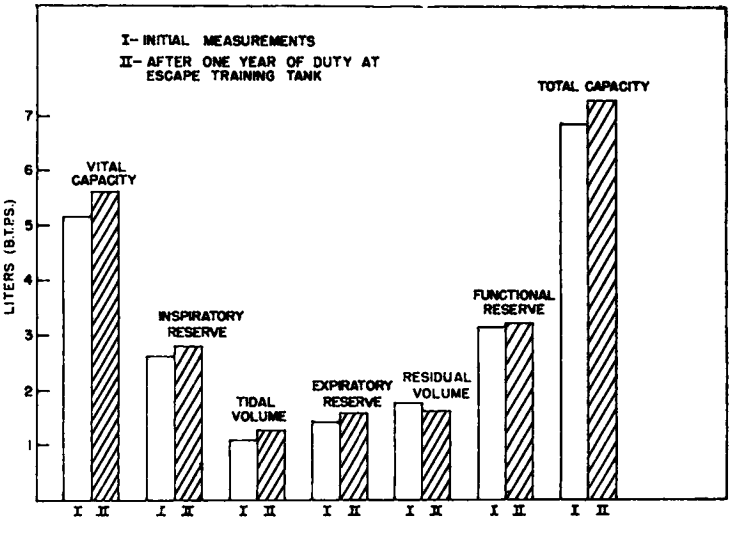

Figure 4.6-6 Effect of Skin Diving on Lung Volume

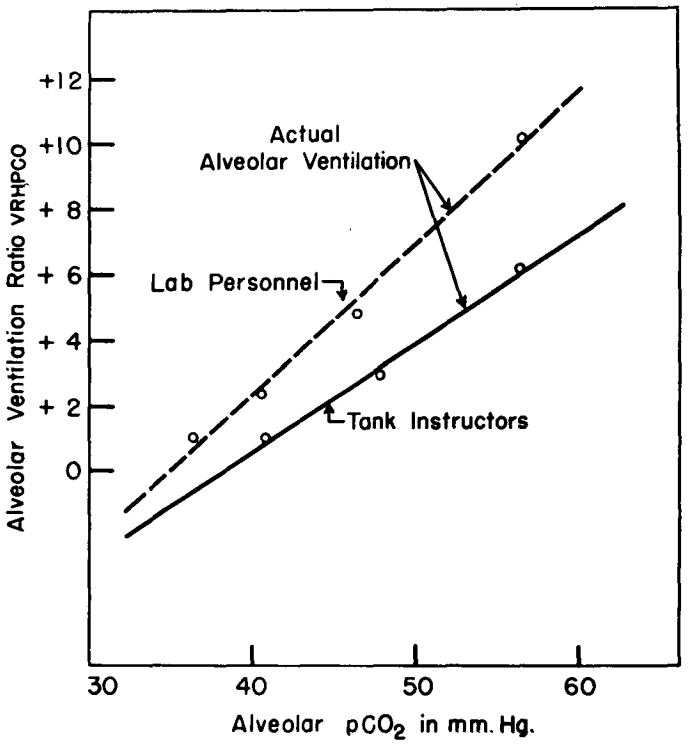

Figure 4.6-7 Ventilatory Response as a Function of Alveolar pCO_2 in Two Groups of Subjects, Laboratory Personnel and Tank Instructors

The same two groups showed corresponding differences in their ventilatory response to low oxygen-nitrogen mixture (10.5% O_2 in nitrogen).[122] In this case low ventilatory response to 10.5 per cent oxygen in nitrogen goes together with low ventilatory response to increased carbon dioxide concentrations, which is in contrast to findings of Dripps, et al,[123] who did not observe such a correlation. Furthermore, tank instructors as a group accepted a significantly larger oxygen debt during 33 minutes of exposure to 10.5 per cent oxygen in nitrogen than the group of laboratory personnel.[124]

These results indicate that besides the adaptation in lung volume, a chemical adaptation takes place inasmuch as the sensitivity to high carbon dioxide and to high oxygen is reduced. It is well known from the studies of Scholander[125] and Irving[126] that diving animals show a lower sensitivity to carbon dioxide than other animals and have the capacity to take up a large oxygen debt. Adaptations in diving men and diving animals seem to correspond rather closely.

The question still remains as to whether this low sensitivity to carbon dioxide has been acquired during the tour of duty. From the lung volume status it became evident that the tidal volume increased during the period at the tank. With the increased tidal volume the respiratory rate decreases. As a consequence, the alveolar carbon dioxide becomes elevated.

In a rather extensive study on 70 subjects we investigated the carbon dioxide response to 1.5, 3.3, 5.4, and 7.4 per cent carbon dioxide. On the basis of a quantitative difference in the ventilatory response to 5.4 per cent and 7.4 per cent carbon dioxide, it was possible to divide a low and a high differential group, Schaefer.(80) These two groups differed already in their respiratory pattern on air. The low-ventilation group has a large tidal volume and a small respiratory rate, while the high-ventilation group has a small tidal volume and a low respiratory rate.

During exposure to 1.5 per cent carbon dioxide this difference in respiratory pattern remains, while during exposure to 3.3 per cent carbon dioxide the response of both groups is pretty much the same. At the higher concentrations, 5.4 per cent and 7.5 per cent carbon dioxide, tidal volume as well as respiratory rate is quantitatively more increased in the high-ventilation group.

As expected, the alveolar carbon dioxide tensions in the two groups show differences. These data were obtained from a series of studies in which the alveolar air was collected with the Rahn sampler and carbon dioxide measured with the Cambridge carbon dioxide meter. The low-ventilation group shows a higher alveolar carbon dioxide tension on air and falls more slowly after transition to air.

From these studies it was concluded that the fundamental difference in the individual response to carbon dioxide is based on different respiratory patterns. The subject with the large tidal volume, a low respiratory rate, and normally higher alveolar carbon dioxide tension shows a lower ventilatory response to carbon dioxide. It is this respiratory pattern which develops or, if already present, becomes more expressed during the activity of the tank instructors.

COMMENTS

DR. RAHN: Thank you very much, Dr. Schaefer. You covered considerable ground during your time concerning breath holding, which agrees rather well with Dr. DuBois' theoretical figures, particularly if we take into consideration Dr. Schaefer's men started with a lowered alveolar carbon dioxide because they hyperventilated, while Dr. DuBois started out with the normal carbon dioxide tensions.

DR. LIVINGSTON: I should like to make a comment with regard to the nervous system in relation to these problems. The nervous system controls respiration and also is the vulnerable target spot to toxicity that was talked about yesterday. The point I should like to bring out relates to the question emphasized by Dr. Yarbrough. How do you explain individual differences?

Now everyone has well in mind the role of different parts of receptor systems and parts of the brain stem that correlate reflexes related to respiratory endeavor in relation to oxygen levels and carbon dioxide levels, and the brain work of Comroe and Madellon refers to carbon dioxide in particular. There are, however, other parts of the nervous system which also are related either to the initiation of these reflexes, that is specific receptor zones within their system, or relays them.

For example, the orbital system of the frontal lobe has to do apparently with relaying response to inhibit respiration when the carbon dioxide level is low. There are other parts that have an opposite kind of action. Head injury very often implicates or most frequently brings damage to this region in its orbital surface of the frontal lobe and in parts of the temporal lobe, likewise related intimately to respiratory activity.

I should like to condense a lot of information in a brief statement to say that the nervous system's capacity to control and regulate these things and the nervous system's vulnerability to epilepsy involve a very complex interrelated matter which makes the explanation of individual differences a very simple matter.

DR. WENDELL: I should like to ask Dr. Schaefer whether he repeatedly exposed the same individual to carbon dioxide and measured the respiratory response?

DR. SCHAEFER: Yes. These people are far out of the range of normal variation. They always have a very low response. We were curious about that so we checked them over a year or more. They always showed this very low response to carbon dioxide. Usually some persons have a higher carbon dioxide response in the morning than in the afternoon, so this is out of range of this diurnal variation.

DR. WENDELL: During the course of drug studies in which we kept the alveolar pCO_2 constant, we made the side observation that the respiratory response to carbon dioxide of the same individual may vary up to 75 per cent on different days and under controlled experimental conditions.

DR. SCHAEFER: We tested these subjects as a rule between 9:00 and 11:00

in the morning to eliminate these diurnal variations in the first place. Then we tested them over quite a time. Several times checked, so we were reasonably sure to have no artifacts in it.

DR. BEAN: I should like to make a comment with regard to carbon dioxide. I think it is very interesting that you might get first one effect, then another. I do not think it is unexpected at all. Some of our effects in high oxygen are also a double effect. I am thinking of the effects on respiration which Dr. Lambertsen mentioned yesterday. I remember years ago in working with high oxygen we had what looked like an apnea for a number of minutes, and I used to think sometimes these animals were dead, but I think it is a case where you had a secondary phase of recession rather than stimulation. I think that is probably part of the explanation, part of the carbon dioxide background.

DR. LAMBERTSEN: I should like to just close these discussions of underwater physiology by thanking all the participants and the visitors in behalf of the National Research Council and the Office of Naval Research. I feel that the contributions all of you have made, both to this formal program and in discussions, have really made this attempt a success. We have missed two men, Dr. Eugene DuBois and Commander Paul Webster. In each case illness has prevented their attending and taking part. I am sure they will be glad to hear the results of the symposium. I am not going to attempt a summary of the varied discussions that have taken place over the past day and a half, excepting in perhaps a very short sentence. I hope from this point on most of us will stop thinking of underwater physiology as being a specialty and think of it as being physiology under water.

5.0 SYMPOSIUM ATTENDEES

LTJG C. F. Aquardo (MC) USNR	Underwater Demolition Unit ONE
LTJG R. T. Arnest (MC) USN	Submarine Squadron SIX
LTJG E. S. Baer USNR	Office of Chief of Naval Operations
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Dr. J.W. Bean	University of Michigan
CAPT A. R. Behnke (MC) USN	Radiological Defense Laboratory
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Dr. Thomas Bradley	National Research Council (Medical)
Mr. H. F. Brubach	National Institutes of Health
Dr. A. C. Burton	University of Western Ontario
Dr. R. K. Cannan	National Research Council (Medical)
Dr. Frank Carpenter	Cornell Medical College
Mr. Alan Claghorn	Linde Air Products Company
Dr. G. F. Clark	University of Pennsylvania Medical School
Dr. John Clements	Army Chemical Center
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Dr. D. Y. Cooper	University of Pennsylvania Hospital
Dr. E. R. Cornish	Army Chemical Center
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CAPT R. H. Draeger (MC) USN	U. S. Navy Mine Countermeasures Station
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Dr. A. B. DuBois	University of Pennsylvania

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Dr. A. B. Otis	The Johns Hopkins University
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Program

Second Symposium on Underwater Physiology

25-26 February 1963

Lecture Room
National Academy of Sciences
2101 Constitution Avenue
Washington, D. C.

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Senior Medical Officer
Experimental Diving Unit

LCDR William H. Hamilton
Office of the Chief of Naval Operations

Monday, 25 February 1963

9:00 am — INTRODUCTION: Present status of individual underwater activities — C. J. Lambertsen

Session 1 — EXTENSION OF DIVING DEPTH AND DURATION
C. J. Duffner, Chairman

9:20 am — Studies of decompression and inert gas-oxygen mixtures — England — H. V. Hempleman — U. K.

9:40 am — Studies of decompression and inert gas-oxygen mixtures — France — de V. Besse — France

10:00 am — Studies of decompression and inert gas-oxygen mixtures — United States — R. D. Workman — U. S.

10:20 am — Prolonged exposure to high ambient pressure — G. F. Bond — U. S.

10:40 am — Panel-Floor Discussion — Duffner, Hempleman, Besse, Workman, Bond

12:00 am - 1:15 pm — LUNCH

Session 2 — PREVENTION AND TREATMENT OF BENDS
H. F. Alvis, Chairman

1:20 pm — Blood coagulability and blood chemistry in bends — L. Barthelemy — France

1:40 pm Modifications of decompression procedure E. P. Barnard U. K.

2:00 pm Hypothermia in the treatment of bends A. Erde U. S.

2:20 pm An analytical development of a decompression computer A. Wittenborn U. S.

2:40 pm Panel-Floor Discussion — Alvis, Barthelemy, Erde, Barnard, Wittenborn

3:20 pm BREAK

Session 3 RESPIRATORY EFFECTS OF INCREASED PRESSURE

H. Rahn, Chairman

3:40 pm Respiratory resistance with hyperbaric gas mixtures A. A. Buhlmann Switzerland

4:00 pm Ventilatory dynamics under hyperbaric states W. Wood U. S.

4:20 pm Influence of increased ambient pressure upon alveolar ventilation E. H. Lanphier U. S.

4:40 pm Panel-Floor Discussion — Rahn, Buhlmann, Wood, Lanphier

5:30 pm ADJOURN

6:30 pm Social Hour — East Lounge, National Press Club, 14th and F Streets, N. W.

8:00 pm Dinner — East Ballroom, National Press Club

9:00 pm Special Presentation — "Diving experiments to extend depth and duration with decreased decompression time."
H. Keller Switzerland

Tuesday, 26 February 1963

Session 4 EFFECTS OF OXYGEN IN DIVING
J. Bean, Chairman

9:00 am Effects of oxygen upon brain metabolism
J. J. Thomas U.S.

9:20 am Histochemical changes produced by high oxygen pressure
N. Becker U.S.

9:40 am Breathing of pressure-oxygenated liquids J. Pegg U.S.

10:00 am Physiological effects of high oxygen pressures C. J. Lambertsen U.S.

10:20 am Film: "Oxygen Convulsion in Man"

10:40 am Panel-Floor Discussion — Bean, Thomas, Becker, Lambertsen, Pegg, Haugaard

12:00 am - 1:15 pm LUNCH

Session 5	INERT GAS NARCOSIS F. G. Carpenter, Chairman		
1:20 pm	Measurement of inert gas narcosis in man	C. M. Hesser	Sweden
1:40 pm	Prevention of inert gas narcosis by drugs and gasses	P. Bennett	U. K.
2:00 pm	A theory of inert gas narcosis	S. Miller	U. S.
2:20 pm	Film: "Inert Gas Narcosis in Man" Panel-Floor Discussion — Carpenter, Wood, Bennett, Hesser, Miller		
2:40 pm	BREAK		
Session 6	OTHER DIVING STRESSES J. Hardy, Chairman		
3:00 pm	Protection against low water temperature	E. Beckman	U. S.
3:20 pm	Acute circulatory effects of immersion	L. H. Peterson	U. S.
3:40 pm	Effects of prolonged diving training	K. E. Schaefer	U. S.
4:00 pm	Panel-Floor Discussion — Hardy, Peterson, Schaefer, Beckman		
4:30 pm	CLOSE OF SYMPOSIUM		

OPEN HOUSE

Morning, 27 February
Naval Gun Factory, Washington, D. C.

9:00 am to 11:00 am — Demonstrations and "Open House" at Experimental Diving Unit, Naval Gun Factory, Washington, D. C.

CDR W. E. Nickerson USN, Officer-in-Charge; CDR R. O. Workman (MC) USN; LT M. Goodman (MC) USN; LCDR G. Enright USN; LCDR F. Barrett USN.

The Experimental Diving Unit will be open for inspection of its unusual facilities and will present exhibits and active demonstrations concerning its work. The pressure vessels and auxiliary equipment will be seen in use. In addition, many types of diving apparatus will be available for inspection. The Deep-Sea Diving School, in the same building, will also welcome visitors. Diving activities of various kinds will be in progress there. A continuous showing of films related to diving problems will also be presented. Together, the Experimental Diving Unit and the Deep-Sea Diving School will constitute an exhibition touching upon almost all aspects of underwater work.