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Christian J. Lambertsen, M.D.
Leon J. Greenbaum, Jr., M.D.
Editors

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ABSTRACT

These proceedings represent a compilation of those papers presented at the Second Symposium on Underwater Physiology, February 25-26, 1963, sponsored by the Office of Naval Research and the Mine Advisory Committee of the National Academy of Sciences-National Research Council.

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.

This symposium continues and complements the discussions presented in the Proceedings of the First Symposium on Underwater Physiology, National Academy of Sciences-National Research Council Publication No. 377, 1955.

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FOREWORD

In 1955, as part of an attempt to arouse interest in the many problems peculiar to the underwater environment, the Panel on Underwater Swimmers of the National Academy of Sciences' Committee on Undersea Warfare joined with the Office of Naval Research to conduct the first Symposium on Underwater Physiology. Since then the field of diving has attracted considerable attention, in extension of the shallow, self-contained diving begun in the throes of World War II, in attempts to increase the depth of human diving and in efforts to extend the duration of deep diving.

While the practice of diving has spread tremendously during the past decade, neither physiological research nor the engineering of apparatus to permit breathing under water has advanced apace. The volume of medical research has recently increased, but the need and the opportunity to obtain new physiological information still appear as great as they did a decade ago.

The Mine Advisory Committee of the National Academy of Sciences and the Office of Naval Research have sponsored this Second Symposium on Underwater Physiology to again call attention to the unusual, difficult and challenging biomedical problems related to work under positive pressures and beneath the sea. These problems and their solution do not relate merely to success in devising physiological and mechanical means of extending the depth and duration of diving. It is at last being recognized that exposure to positive pressures in laboratory and clinical treatment situations offers useful means of modifying physiological and pathological processes in man. It can be expected that interest in the hyperbaric environment will further increase, quite in addition to the continued concern for improving the capacity of the diver to perform useful work.

This Symposium has provided an opportunity for investigators from several countries, including the United States, Great Britain, Scotland, France, Sweden and Switzerland, to exchange information and concepts. These Proceedings comprise the individual papers presented by this distinguished international group, as well as the discussion of major topics. The active formal meetings were supplemented by demonstrations of diving techniques and equipment displays at the U.S. Navy Experimental Diving Unit.

On behalf of the Mine Advisory Committee and the Office of Naval Research, the Symposium Planning Group would like to express its sincere appreciation for the valuable contributions made by those participating in the scientific sessions. It would also like to recognize with gratitude the diligent and skillful technical editing assistance provided by Miss Eleanor Jones of the University of Pennsylvania Laboratory of Pharmacology, the competent execution of the laborious task of transcribing the manuscripts and discussions by Mrs. Maxine Sheesley of the Mine Advisory Committee Staff, and the valuable assistance provided by Miss Susan Kronheim of the Physiology Branch of the Office of Naval Research in the many details of planning and executing the Symposium.

The Symposium Planning Group

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PRESENT STATUS OF UNDERWATER PHYSIOLOGY

C.J. Lambertsen
Department of Pharmacology
University of Pennsylvania
Schools of Medicine
Philadelphia, Pennsylvania

For our hosts, the Mine Advisory Committee of the National Academy of Sciences and the Office of Naval Research, I welcome all of you to the Second Symposium on Underwater Physiology. May it enjoy the interest and the success of the first symposium[1,1a].

There are many reasons why our combined attention should again be brought to bear upon the physiology of exposure to positive pressure and the underwater environment. Diving is an expanding field of practical endeavor, not only for military purposes, but also in scientific submarine explorations, oceanographic studies and marine biological research activities. While amateur interest in diving has not slackened and will probably be sustained forever, I detect an increasing desire in civilian divers to put their interest in diving to useful purpose.

Interest in the interrelated physiological effects of underwater existence is also increasing, at least apace with the expansion in practical applications of diving methods. The peculiar physiological stresses of diving are of evident interest to naval medical laboratories throughout the world. There has been a purposeful and welcome effort by the naval organizations of several countries to advance physiological studies in their own laboratories, and by support of research in universities.

Finally, with the passage of time, investigators have become more and more interested in adapting to positive pressure experimentation the excellent quantitative methods which have been developed for use in sea level studies. Many investigators have discovered that the conditions of diving offer attractive opportunities as tools for physiological research; others are discovering the implications of positive pressure for problems of general medicine[2]. The result of this increase in interest, effort and quantitative study can only be an improvement in the comprehension of the positive pressure environment and in the capacity to work under water.

With these thoughts in mind, where do we now stand in the evolution of diving physiology? Have we truly come a long way from the first shallow penetrations with the lungs full of "held" air or from the primitive efforts to carry a supply of respirable gas beneath the surface? It is worth realizing that while practical progress has been tremendous and physiological advance considerable, even the physiological consequences of breath-holding at various pressures and with various gases have only recently begun to be understood[3,4,5,6]. Very few of the biomedical problems peculiar to diving have been so well studied that we can afford to slacken the pace of their investigation.

Many countries represented here have contributed to our present practical and theoretical information. Years ago, helmeted divers, breathing air compressed to the working pressure, gained tremendously in two important ways from studies by our British colleagues. Haldane cleared the minds of these air-breathing divers by insisting upon the ventilation of their helmets in proportion to the depth of diving[7]; this diminished the high tension of inhaled carbon dioxide which, although unrecognized as such, had been a limiting factor in diving with compressed air. Carbon dioxide still remains important to diving physiology in a great variety of ways.

A second great contribution of English science to diving you also know. This was the successful effort to introduce a logical procedure for decompressing tunnel workers following exposure to compressed air[8]. This theoretical contribution was extended by the subsequent, laborious work of naval laboratories in the United States and England, and led to over a half century of successful diving with compressed air and helium-oxygen mixtures[9,10].

Now, partly because of the practical extension by the French of the use of air-breathing apparatus by free swimmers[11], even compressed air diving provides new problems of decompression physiology which have not been completely solved[12]. These are related to the fluctuating and highly variable patterns of diving depth and also to repeated exposures to increased pressure without complete removal of the excess inert gas accumulated during prior dives. Because of the practical desirability of such forms of exposure, these may forever be among the most common problems of diving medicine.

Thirty years ago, to extend diving depth beyond the levels at which compressed air stupified the diver, gas mixtures other than air were studied and inert gases other than nitrogen were used. This led to the meticulous studies of helium-oxygen mixtures by naval investigators in this country[10,13], the studies with hydrogen in Sweden[14], the practical application of N_2-O_2 diving by the British during World War II, the more recent laboratory studies with nitrogen-oxygen mixtures in England and the United States[15,16], and to a slowly progressing interest in multiple gas mixtures[17,18,19]. Exposures of extreme duration are now also receiving attention[20,21]. We should now be concerned not only with studies of unusual gas mixtures, but also with the problems basic to purposeful alternation of exposure to pure oxygen with exposure to an inert gas-oxygen mixture to improve the rate or safety of decompression[1,19].

Throughout the history of diving, the occurrence of nitrogen narcosis has kept alive the unresolved question of its mechanism. Concepts and studies of inert gas narcosis concern pharmacologists and anesthesiologists as much as they do diving physiologists. Since the earliest recognition of nitrogen intoxication, many concepts of inert gas narcosis have been advanced and subjected to detailed study. In medicine and in diving the mechanism whereby any gaseous agent produces narcosis continues to excite great practical and theoretical interest[22,23,24].

In all of these investigations, whether of bends, narcosis, carbon dioxide effects, or respiratory problems, the physiological effects and toxicity of oxygen itself run as a web of connecting threads. My memory is remarkably clear

concerning one brief episode in the long-term evolution of diving. This was the period of extensive practical use of oyxgen in diving[11] and of studies of pure oxygen effects on man in Italian, British and U.S. laboratories during World War II[25,26] Out of these efforts came considerable information concerning the tolerance of men to increased Po_2, but this information is, even now, so incomplete that diving with oxygen alone and with inert gas-oxygen mixtures is handicapped. Recent studies with inert gas-oxygen mixtures have again focused attention upon carbon dioxide and oxygen by indicating that incapacitating, carbon dioxide autointoxication can occur even when nitrogen-oxygen mixtures are used in open-circuit breathing systems during strenuous work[27]. Such observations offer partial excuse for the still evident uncertainty regarding the roles and interactions of carbon dioxide and oxygen producing what twenty years ago was aptly labeled "Shallow Water Blackout"[28].

For a time the diminished use of pure oxygen in peacetime diving resulted in an unfortunate lack of attention either to the important implications of high oxygen pressures to other forms of diving or to the physiological gains in decompression by inspiring gas mixtures with low or zero tensions of inert gas. Increased interest in the application of oxygen decompression to shorten or improve the safety of air or mixed gas diving will require continued study of the physiological as well as the toxic effects of oxygen.

It is evident that while most of the individual problems of the underwater environment are now well recognized, they are not yet adequately solved. Today, with renewed interest in extending the capacity of man for extra-atmospheric existence, it should be emphasized that the research required for penetration of the seas of this earth deserves attention at least comparable in quality and degree to that for human existence in the space beyond earth's atmosphere. This is an increasingly exciting field of work. Research in underwater physiology is no longer the slowly moving stepchild of medical research. Questions and the methods of answering them are springing out of many civilian and military laboratories, and, as already mentioned, the implications of some of these studies to general medicine and surgery are being recognized.

With this renewed interest, what is the state of our information and our concepts? What do we know and what experiments should now be done? Let me join you in the audience, give attention to our first session, and find out.

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TISSUE INERT GAS EXCHANGE AND DECOMPRESSION SICKNESS

H. V. Hempleman
Royal Naval Physiological Laboratory
Alverstoke, Hants., England

Current ideas on tissue saturation with inert gases were largely initiated by Haldane[1] in his attempt to construct successful decompression schedules. Since then much further practical work has been carried out by Jones and his associates[2] using radioactive tracer techniques, and a very detailed mathematical treatment of various tissues of differing capillary densities appears to lend convincing support to the present ideas. This analysis was performed by Roughton[3] and the basic model used was a central cylindrical capillary responsible for a concentric cylinder of tissue. In brief, the position now reached with these ideas may be summarized as follows:

> The inert gas which is supplied to the tissue disperses itself uniformly over the tissue space because diffusion is very rapid between the capillaries, and hence the inert gas tension of the blood being removed is truly representative of the whole tissue inert gas partial pressure. Defining:

P_o = inert gas tension of blood supplying tissue

P = inert gas tension of blood leaving tissue

V = rate of blood supply per unit tissue volume per minute

S_B = solubility of inert gas in blood

we see that

P_oVS_B = rate of supply of inert gas to tissue

PVS_B = rate of removal of inert gas from tissue

and from this

$(P_o - P)VS_B$ = rate of accumulation of inert gas in tissue.

Also defining

S_T = solubility of inert gas in tissue

$S_T(dP/dt)$ = rate of change of gas content in tissue.

Since the rate of accumulation must equal the rate of change in tissue content we have the equation:

$$S_T(dP/dt) = (P_o - P)VS_B$$

letting $k = VS_B/S_T$ and solving we have

$$P = P_o(1 - e^{-kt}).$$

Thus the rate of saturation of a tissue depends only upon the blood perfusion, V, and the ratio of the solubility of inert gas in the blood to its solubility in tissue, S_B/S_T. On this theoretical basis most analyses of whole body uptake and elimination of inert gas have taken place.

In a paper from Groupe d'Etudes et de Recherches Sous-Marines at Toulon[4] after reviewing the practical and theoretical discussions regarding tissue inert gas exchange the author decides to support the perfusion mechanism and to reject any place whatsoever to diffusion mechanisms. It is my intention to try to demonstrate that this can only be regarded as an incorrect appraisal of the true situation.

Let us suppose that a subject commences suddenly to breathe a pressure of inert gas of magnitude P_o atmospheres and that previous to this time he had no inert gas whatsoever in any part of his body. It is clear from very simple considerations that after a few minutes of breathing the new gas pressure there will exist certain parts of the body where the concentration of the inert gas is high and certain parts of the body where the concentration is non-existent or very low. The existence of concentration gradients will cause dissolved gas to flow down the gradients. Such flow will be largely influenced by diffusion mechanisms and one must decide whether such inter-tissue diffusion flow is going to compete in any way with the perfusion flow of dissolved gas into the respective tissues. Resorting to microscopic situations such as those examined by Roughton will not prove very effective as a means of yielding quantitative considerations. Consequently a new model for discussion will be proposed. It must of course be realized that all these models represent completely idealized situations and are constructed solely for the purpose of extracting very gross information.

Represented in Figure 1 are two tissues of very different vascularities. The vascular tissue ends abruptly at a flat surface and a relatively poorly vascularized tissue commences. Suppose that the perfusion of these two tissues began some minutes ago with blood at a gas tension P_o atmospheres. Suppose further that there exists a uniform gradient of concentration from this highly vascular region to a plane 1 cm. inside the slow tissue, AA' on the diagram. Consider a slice of tissue at AA' of the length 1 cm. and with a cross section measuring 1 mm. x 1 mm. This will be considered as a piece of poorly vascularized tissue the center plane of which is 1 cm. away from a high concentration P_o. If both the very vascular and poorly vascular tissues are of a "watery" nature it can be stated that at body temperature approximately 1.0×10^{-5} cc. of nitrogen will flow per sq. cm. per atmosphere pressure gradient through the plane AA' per minute. The amount therefore flowing through the section on the diagram will be 1/10 of this, i.e., 1.0×10^{-6} cc. of dissolved nitrogen per minute per atmosphere pressure. The amount reaching the tissue via the blood stream can also be estimated. Taking 1 capillary per cubic millimeter there will be 10 capillaries

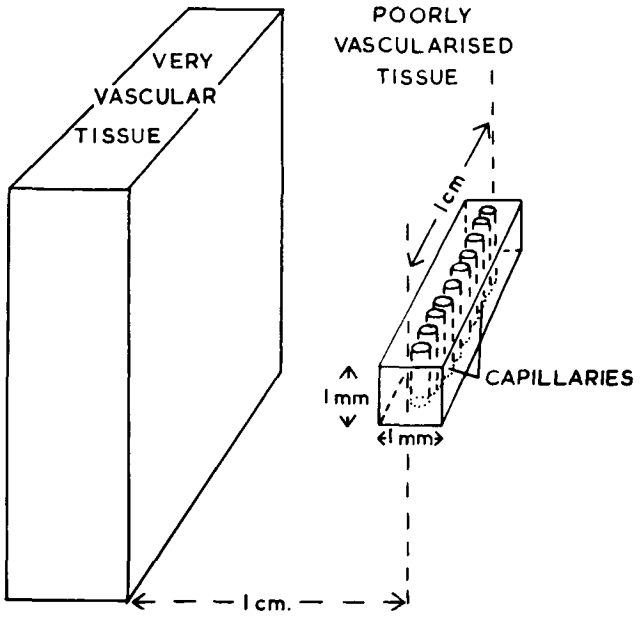

Figure 1. Tissue Saturation with Inert Gas Perfusion-Diffusion Complex Situation.

in the slice of tissue under consideration. Suppose each of these are 8 μ in diameter and that the flow of blood down them is 1 mm per second. Taking the solubility of nitrogen in blood as 0.012 cc per cc of blood per atmosphere pressure it is seen that the rate of arrival of nitrogen via the blood flow in P_o x 3.6 x 10^{-7} cc per minute. Examination of these figures suffices to show that the diffusion gradient is supplying gas molecules which for a 1 atmosphere per cm pressure gradient would require a P_o value of nearly 3 atmospheres. In such situations as this one the inter-diffusion processes will tend to dominate the kinetics. The poorly vascularized tissue will have rapid and slow components to its uptake curve, with the slow components predominating, whereas the vascular tissue will have fast and slow components with the rapid components dominating. This then will be the general picture derived from an examination of this particular type of tissue situation. When the vascularity of the two tissues does not differ by a great deal, or when both tissues have large perfusion rates then the part played by inter-diffusion will become very much less important, and will only be noticeable at the interface between the two different capillary densities. When the vascularity of a tissue is non-existent and the adjoining tissue is a highly vascular one, then provided the avascular tissue is 3 or 4 mm thick, this tissue will be entirely diffusion limited for its uptake and elimination of inert gases. Such a situation occurs in the cartilage associated with knee joints, where the completely avascular layer of cartilage is overlaid with the very vascular synovial membrane, or again there is the relatively vascular spinal cord which treads its way through cartilagenous discs, teninous inserts and bone. In fact these latter situations look to be exactly the sort of situations with which one is principally concerned in decompression sickness research. The main troubles which occur as a result of inadequate decompression are pains in and around joints, particularly knee joints, and in the more severe cases there are paralyses undoubtedly caused by emboli in, or close to, the spinal cord.

Thus the idea formed that perhaps in decompression sickness the main mechanism was a diffusion limited one. Initially this was also apparently well supported by the following experimental evidence. If one takes a large animal such as a goat as the experimental subject then the manifestations of decompression sickness which occur after inadequate decompression are very similar to those shown by man, i.e., they get a pain in a limb (a bend) which causes limping,

or in more severe cases they get emboli in the spinal cord causing paralysis of the hind legs. Now if a goat is rapidly compressed to a pressure P feet of sea water, is held there for a time t minutes, and then is decompressed in 150 seconds back to atmospheric pressure, it is possible to choose P and t, which are of course independent variables, such that for a given t there is a P value which just produces a mild bend on return to atmospheric pressure. This value of P is called the bend threshold for this particular animal for this particular t value. In Figure 2 can be seen the curves obtained from doing hundreds of such threshold

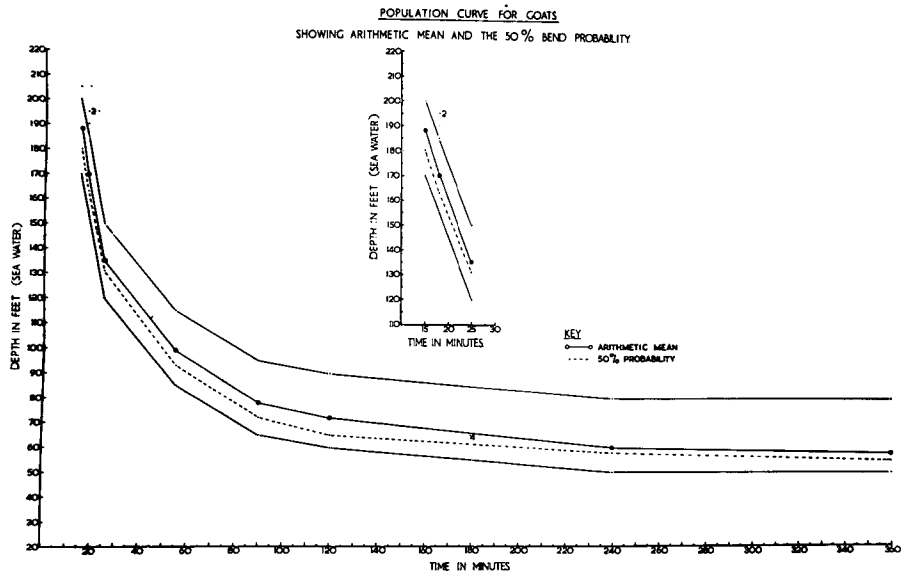

Figure 2.

dives on very many different goats. The two outer black lines represent the limits of the population. The bottom line represents the most sensitive results obtained and the upper line represents the most resistant results. In between (also a continuous black line) is shown the arithmetic mean. It can be seen that the arithmetic mean is nowhere near the middle of the range of sensitivities and hence it is correctly deduced that for a given duration of exposure the sensitivity of the population is not distributed normally but in a very skew manner. Most animals are close to the average but a few highly resistant animals give a tail to the distribution. In view of the skewed nature of the distribution the median average goat will be discussed. It is immediately apparent and not in the least surprising that for a short t there corresponds a large P value, and that for a large t there is a comparatively small P value. This suggests that perhaps a constant quantity of excess gas is involved in producing the threshold bends observed in all these animals. If now this idea is coupled with a diffusion-like inert gas saturation process then a relationship of the form $P_t^{1/2} = K$ is to be expected, provided the t value is not too great. As can be seen from Table I $P_t^{1/2}$ is quite constant over a considerable range of t values. The P value used is that for the median average goat. Thus it would appear that there exist good

TABLE I

DATA FOR GOATS SHOWING RANGE OF CONSTANCE FOR $P\sqrt{t}$

Median Pressure (P) in feet	Duration t(mins)	$\sqrt{t}$	$P\sqrt{t}$
180	15	3.87	697
163	18	4.24	691
131	25	5.00	655
93.2	50	7.07	659
71.5	90	9.49	678
65.0	120	10.9	708
57.0	240	15.5	883

grounds for regarding the kinetics of inert gas exchange, insofar as they affect decompression sickness, as being diffusion limited. In fact if one were merely interested in an equation to represent these results, a diffusion-like mechanism would represent them very accurately, and could well be used as a basis for analogue computer work. However at this stage it was decided to pursue the aetiology of "bends" rather than just finding some convenient mathematical formulation.

This led to an examination of whole body curves for the uptake and elimination of inert gases and gave a somewhat surprising result. If a subject saturated with air at atmospheric pressure is given pure oxygen to breathe, then of course the dissolved nitrogen which was in his body is eliminated giving a whole-body inert gas elimination curve. Now the quantity of gas eliminated when plotted against the square root of t gives an excellent linear plot for the first 90 minutes. The data shown here are from Lundin[5] but data by Behnke[6] would equally well give such a relationship. In fact it is worth noting that the helium elimination curve of Behnke's study also gives a linear plot with $t^{1/2}$, again up to about 70% saturation. Thus the whole body gas exchange curve can also be regarded as entirely analogous to a diffusion limited mechanism, although it is beyond dispute that this cannot be the case. The fact that the whole body curves have a diffusion-like appearance when the underlying mechanism cannot be mainly diffusion limited shed doubts on the deductions made previously in regard to the meaning of the $Pt^{1/2}$ relationship established in the decompression sickness results. Consequently experimental facts must be sought elsewhere in order to clarify this.

The next series of investigations concerned the role of oxygen pressures in decompression sickness and were planned as follows. Goats were rapidly compressed to an air pressure equivalent to P feet of sea water; at this pressure they were maintained for t minutes, and then were decompressed in 150 seconds back to atmospheric pressure. Two t values were used in the first experiments (t = 18 minutes and t = 180 minutes). The animals were subjected to such a P value that on return to surface they just exhibited a mild attack of the "bends."

Some of the results are summarized in Table II. Goat 63 for instance did an exposure to an air pressure of 155 feet for 18 minutes and on return to surface in 150 seconds just received a mild attack of "bends." This bend threshold value has been called D in the Table. If now this animal is subjected to a pressure

TABLE II

COMPARISON OF GOAT BEND THRESHOLDS
ON AIR (D) AND AIR PLUS OXYGEN (D - 15 + D.O_2)

Goat No.	Time of Esposure (mins)	D	D - 15 + D.O2
70	18	160	165
63	18	155	165
54	18	165	195
66	18	165	175
70	180	65	80
54	180	95	105

D - 15 feet of air pressure for 18 minutes it will never exhibit an attack of the "bends," and such a dive is perfectly safe for it. However in the experiments outlined in this Table oxygen was added to the D - 15 value until on return to atmospheric pressure the animal once again exhibited a mild attack of the "bends." As expected, the depth of the oxygen-rich mixture was greater than on the air, ranging from an extra 5 feet to an extra 30 feet, on this number of animals. Two of these animals were also tried on an exposure of 3 hours duration. As may be seen the extra oxygen to be added to the threshold air dive is within the same limits, 10 feet extra in one case and 15 feet extra in the other. Thus adding oxygen to replace nitrogen is, as is well known from standard diving practice, a good exchange. It is necessary to emphasize that these experiments demonstrate beyond question that oxygen pressures cannot be ignored from the decompression sickness standpoint. There are many investigators who concern themselves solely with the inert gas pressure of the gas being breathed. This can be seen to be an oversimplification. The further point to be noted is that oxygen is equally effective at both ends of the time scale. Now the generally accepted explanation for the protection afforded by substituting oxygen for inert gas is that oxygen cannot only be eliminated by the normal processes available to inert gas but that it is metabolized away in situ and hence bubbles of oxygen can either never grow, or if they do grow to a painful size then the effect will probably be transient. If this explanation is accepted then the very beneficial effects of substituting oxygen for inert gas in the long exposure dives are somewhat puzzling to understand on conventional ideas. Only tissues with very long half times are involved in bends exhibited after prolonged exposures to pressure. It follows then that these tissues must be very avascular and consequently very low in their metabolic requirements of oxygen. Now oxygen is much more soluble than nitrogen or helium in both fat and water, and if it were not for the metabolic

usage it would represent a very unsuitable gas on which to dive for prolonged periods. The fact that it is not only not an unsuitable gas for prolonged dives but in fact is far better than nitrogen or helium implies a fairly rapid rate of removal and this of course is impossible in an avascular tissue with a long half time, consequently the bubble must be lodged in a vascular tissue with a fairly high oxygen usage. This tissue must adjoin tissue which is comparatively avascular, and whether the bubble grows or regresses depends upon the outcome of the avascular tissue off-loading its excess gas into the bubble (or bubbles) and the vascular tissue eliminating via the blood stream and also by metabolic processes in the case of oxygen, the gaseous contents of any such bubbles, which are formed. This is in fact the inter-diffusion situation envisaged earlier in this paper.

One further fact is now relevant. It has been shown that although animals exhibit mild bends after an inadequate decompression procedure it is quite impossible to predict whether the bend will appear on the right side or the left side. An animal will behave in this matter as though it were completely symmetrical and the bends are as frequent on the left side of the body as on the right side. This random nature of the bends strongly suggests that the bends are initiated by a mechanism common to both sides of the body. This would implicate either the central nervous system or the blood. On examination of the data the blood seems the most likely source of the bubbles. The picture emerges then that as a result of inadequate decompression, bubbles form in the blood and are carried around to various tissues. Only those bubbles which lodge in tissues adjacent to reservoirs of dissolved gas can continue to grow via diffusion from these slowly saturating tissues. This concept of the aetiology of the "bends" appears to explain satisfactorily all the major accepted facts in regard to decompression sickness and implies the necessity for re-examination of the significance of inert-gas exchange measurements.

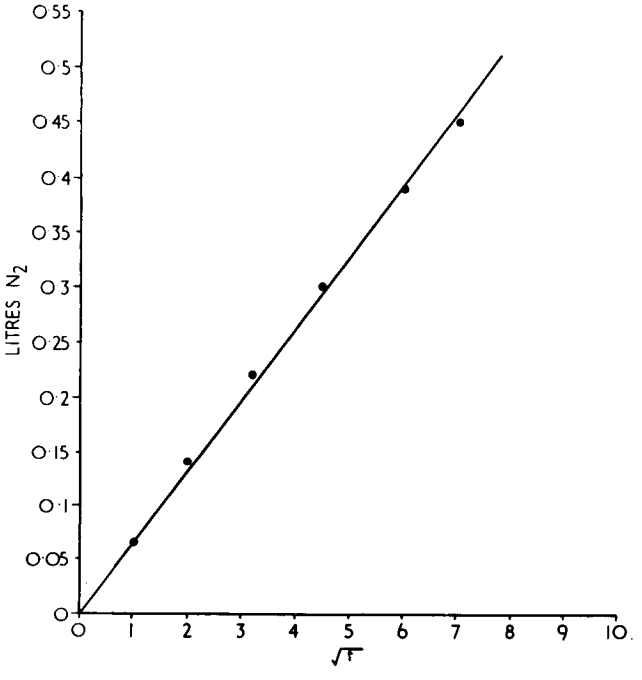

Figure 3. Nitrogen Elimination during Oxygen Breathing

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STUDIES OF DECOMPRESSION

F. Besse
Lieutenant de Vaisseau, French Navy
Groupe d'Etudes et de Recherches
Sous Marine (GERS)
Toulon, France

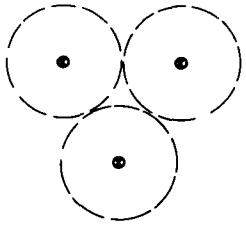
To calculate a decompression procedure, the French Navy has chosen a method of calculation very classical, simple and almost the same as the method used by the U.S. Navy. However, simplicity and U.S. examples have not been the only reason for our choice; we have also studied the laws of solution of inert gases in the human body and the laws of formation of gaseous bubbles which cause decompression sickness. This calculation method was used in 1958 to establish new tables for air diving specially fitted to SCUBA diving, and then last year was applied to some experiments of deep diving with oxygen-helium mixtures and semi-closed circuit SCUBA.

The calculation method is that of Haldane and can be demonstrated by the main hypothesis: "The rate of change of the tension of inert gas dissolved in a tissue is proportional to the difference between the pressure of this gas in the mixture inhaled and the tension of inert gas dissolved."

i.e., $$\frac{dp}{dt} = k\,(P - p)$$

Such a hypothesis supposes that the tension of dissolved gas is uniform in the particular tissue. In order to verify this fact, it is necessary to study the laws of diffusion of inert gases in human tissue. Dissolved gases are transported in the human body by the blood. We have to study the diffusion from the capillaries into the tissue itself.

Each capillary can be represented by a cylinder whose length is infinite in regard to its radius and we can suppose it irrigates a coaxial cylinder whose diameter is equal to the mean distance between two open capillaries. The diffusion law of Fick applies here.



$$\frac{\partial p}{\partial t} = D\left(\frac{\partial^2 p}{\partial x^2} + \frac{\partial^2 p}{\partial y^2} + \frac{\partial^2 p}{\partial z^2}\right)$$

which by axial symmetry is

$$\frac{\partial p}{\partial r} = D\left(\frac{\partial^2 p}{\partial r^2} + \frac{1}{r}\,\frac{\partial p}{\partial r}\right)$$

Figure 1.

where r is the distance to the axis of the cylinder. Integration of this equation is very complicated but it can be done. This problem was studied in 1952 by Roughton[1] who resolved it with precision and a perfect mathematical rigor. I do not intend to expose you to the details of calculations but only the results which are very interesting.

We know D, the average diffusion coefficient of nitrogen in the human body, which is 10^{-5} sq cm/sec. The radius of capillaries is about 4×10^{-4} cm. Roughton demonstrated that diffusion rate was very rapid, with half-time of .01 to 100 seconds, a function of the distance between open capillaries. From diving experiments we knew we had to consider tissues whose half-time numbered in minutes, that is about one hundred times more.

We can conclude that the diffusion of dissolved inert gases from the capillaries is so rapid that we can consider the concentration of dissolved gas uniform in the tissue between the capillaries. All this justifies the hypothesis and calculation method of Haldane. The tension of gas dissolved in a tissue is a function only of the solubility of gas in this tissue and of its blood circulation.

The body is formed of different tissues, each of them characterized by a time constant "k" or by a half-time "T," where $T = \text{Log}_e 2/k$.

The other main problem is that of supersaturation with dissolved gas, which exists during ascent of the diver toward the surface. The critical supersaturation can be defined by either of two criteria:

1) Supersaturation gradient, which is the difference between the dissolved gas tension and the hydrostatic pressure.

2) Supersaturation ratio, which is the ratio of the dissolved gas tension to the hydrostatic pressure.

Attempts have been made to justify utilization of the gradient definition by applying the idea of surface tension, so well defined by Harvey[2]. Due to forces of surface tension, a gaseous spherical bubble in a liquid has an inside overpressure (ΔP) relative to ambient pressure. It can be expressed:

$$\Delta P = \frac{2\sigma}{r}$$

where σ is the superficial tension between the gas and the liquid and r is the radius of the bubble. For example, an air bubble in water, with a critical supersaturation gradient of one atmosphere, produces a spherical bubble with a radius of 1.5 microns (which is very similar to the size of capillaries) and tempts us to use the concept of a critical supersaturation gradient. However, a more thoughtful study shows that it is impossible for such bubbles to stay in equilibrium in the blood. If the radius, r, of the bubbles decreases, the pressure inside the bubble will increase and then there will be a diffusion of gas from the bubble to the blood (from gaseous to dissolved phase) resulting in disappearance of the bubble. If the radius of the bubble happens to increase, pressure inside will

decrease. There will be a diffusion from the dissolved to gaseous phase and the bubble will increase in size. Equilibrium established by the equation $\Delta P = (2\sigma)/r$ is an unstable equilibrium and practically such critical bubbles cannot exist. If gaseous bubbles, small as they are, are free to circulate in the blood, then there is one chance in two that they will increase in size and will be the cause of decompression sickness.

Utilization of the concept of critical supersaturation ratio is not common, however, Harvey's studies justify it well. Harvey demonstrated that it was necessary to suppose existence of permanent gaseous nuclei. Without them it is impossible to get gaseous bubbles "de nihil" with the rather small pressure changes encountered during a dive. As long as the diver is on the bottom, the tension of inert gases dissolved is smaller than hydrostatic pressure. The gaseous nucleus must have a concave surface, which is possible if we imagine this nucleus in a fissure of a vessel wall or in intracellular space as in Figure 2A.

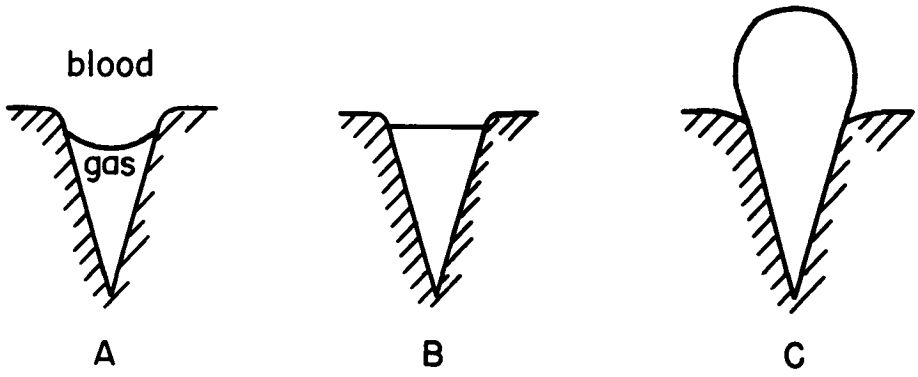


Figure 2.

During ascent of the diver toward the surface, hydrostatic pressure decreases and gaseous nucleus volume increases. When hydrostatic pressure becomes equal to the tension of inert gases dissolved, the separating surface between gaseous nucleus and blood is a plane (Figure 2B). Hydrostatic pressure goes on decreasing, dissolved gases are in supersaturation and the surface of gaseous nucleus becomes more convex (Figure 2C). One can easily imagine that when the nucleus volume has doubled, or tripled, it will separate from the vessel wall to form a bubble, more or less spherical, free in the circulating blood and resulting in decompression sickness.

That is why, in our decompression calculations, we have chosen the idea of critical supersaturation ratio. Investigators in the U.S. Navy think this ratio depends on the depth of the decompression stop. This has not been proven, and we consider that critical supersaturation ratio is independent of depth and duration of the dive, and is only a function of half-time of the tissues and the type of inert gas.

NEW FRENCH DIVING TABLES

In 1958 we calculated, experimented and put into service new air diving tables, specially fitted to SCUBA diving. They are limited to depths of 40 meters (130 feet) and to durations of one to two hours, depending on the depth. The most rapid tissues can bear supersaturation ratios larger than the slowest tissues. We have seen that for these small depths it was not necessary to take into account the rapid tissues for our calculations. Therefore, this table was calculated with tissues having half-times of 40 minutes, 75 minutes and 120 minutes. Having knowledge of the U.S. Navy studies of 1955, we have chosen for the relative critical supersaturation ratio, the values of: 2.3 for the 40 minute tissues and 2.0 for the 75 and 120 minute tissues. After completion of our experiments, the rate of ascent was fixed at 20 meters/minute.

The results are a diving table showing a decompression slightly shorter than the U.S. Navy table for short dives, which are the most frequent in SCUBA dives, and comparable for middle dives. This table was proved by 350 experimental dives, and has been used in the French Navy for four years without any incident.

DEEPER SCUBA DIVES WITH OXYGEN-HELIUM MIXTURES

When we intend to dive deeper, it becomes necessary to improve Haldane's method in order to follow with greater precision the rate of change of the dissolved gases during the descent and the ascent of the diver. The following equations are involved:

$$\frac{dP}{dt} = k(P_I - P) \qquad (1)$$

When P_I is constant, this can be integrated to

$$P = P_o + (P_I - P_o)(1 - e^{-kt}) \qquad (2)$$

where
P = tension of inert gas in tissue
P_o = initial tension of inert gas in tissue
P_I = tension of inert gas inhaled
k = time constant of tissue = $(\log_e 2)/T$

Equation (1) can also be integrated when P_I is a linear function of time, that is

$$P_I = P_{I_o} + P_I't$$

with
P_{I_o} = initial tension of inert gas inhaled
P_I' = constant rate of change of P_I

to give

$$P = P_o + P_I't + \left[P_{I_o} - P_o - \frac{P_I}{k}\right]\left[1 - e^{-kt}\right] \qquad (3)$$

We shall use equation (3) during the descent and ascent of the diver.

We must also choose which half-time tissues to consider in this type of calculation. It would be ideal to consider the whole family of tissues with half-times ranging between minutes and hundred of minutes, i.e., to study the envelope of a family of exponential functions. However, its mathematical formulation is too difficult to handle. That is why we shall study separately some tissues. Since we use exponential formulas, it would be logical to choose those tissues following a geometric progression, viz., k = 0.5, 0.1, 0.02 and 0.004. The first tissue, the more rapid, can be neglected in the calculations. We can demonstrate that it eliminates dissolved gas in proportion to the ascent, when the ascent rate is 20 meters/minute. As usual, we shall choose the value of 120 minutes for the slowest tissue. The study of critical supersaturation ratios has shown us we have to take into account a tissue with a half-time of 60 minutes. In conclusion, we decided to use in our calculations the tissues:

k = 0.1	where T = 7 minutes.
k = 0.0231	where T = 30 minutes.
k = 0.01155	where T = 60 minutes.
k = 0.00577	where T = 120 minutes.

It is necessary to determine what are the supersaturation ratios each tissue can support when the inert gas is helium. These ratios do not depend on the depth of the dive. It is easy to calculate them from the no-decompression experimental dives. The U.S. Navy has done many experiments indicating, for various depths, the longest dives which permit ascent to the surface without decompression stops. The calculation of the tension of helium dissolved in each tissue, when arriving at the surface, indicates the supersaturation ratio. For deep dives, when the stay on the bottom is very short, we have to take into account the exact rate of descent and ascent, that is we have used equation (3). We have made these calculations and have seen that:

1) Between 12 and 20 meters, the dive is limited by 60 minute tissue, which can support a supersaturation ratio of 1.8.

2) Between 20 and 35 meters, the dive is limited by 30 minute tissue, which can support a supersaturation ratio of 2.

3) Between 35 and 55 meters, the dive is limited by 7 minute tissue, which can support a supersaturation ratio of 3.

Having the knowledge that the duration of a dive is not limited at 11 meters, we can conclude that the critical supersaturation ratio of 120 minute tissue is 1.7.

We have programmed all the above data on an IBM 1620 computor which now gives us any decompression schedule we need. The computor calculates the

tension of dissolved helium in each of the four tissues during the following phases:

1) Preoxygenation before the dive, if needed.

2) Descent with a constant rate, usually 30 meters/minute, and a change of the percentage of oxygen in the mixture at definite depths.

3) Stay on the bottom.

4) Ascent at a rate of 20 meters/minute, with a change of the percentage of oxygen in the mixture at definite depths.

The computor indicates the duration of the stops for decompression, with an interval of 3 meters. Usually the diver inhales pure oxygen from the time he reaches 15 meters to the surface.

We began to verify this calculation method about one year ago. In France we have a very good semi-closed circuit SCUBA, the "DC55." This apparatus was made by G. E. R. S., the "Groupe d'Etudes et de Recherches Sous-Marines." It has been used for five years in shallow waters, and we verified its performance at 150 meters in a dry chamber. We have begun the verification of the decompression calculations which I have shown you by some simulated dives at 100 meters. For example, we have several times made the following dive (shown in Figure 3).

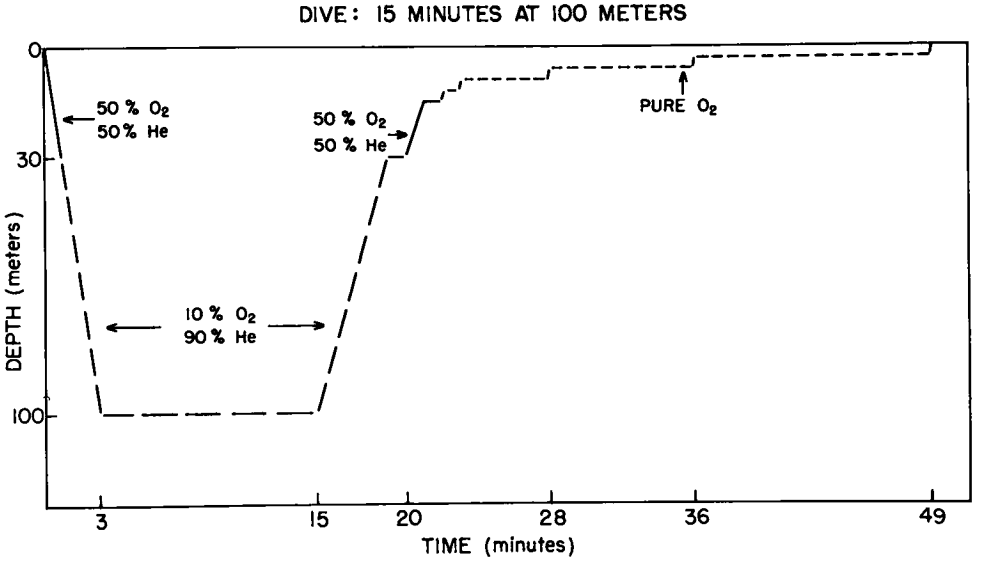


Figure 3.

1) Descent to 30 meters with a mixture of 50 per cent oxygen with 50 per cent helium, then change to a mixture of 10 per cent oxygen with 90 per cent helium.

2) On the bottom at 100 meters at the minute 3.

3) Stay on the bottom at 100 meters till the minute 15.

4) Ascent with a rate of 20 meters/minute.

5) At 30 meters, one minute stop to change the gas mixture.

6) At 15 meters, one minute stop to change the mixture and begin to inhale pure oxygen.

The decompression stops then used were: 1 minute at 12 meters, 5 minutes at 9 meters, 8 minutes at 6 meters and 13 minutes at 3 meters. This is a total ascent and decompression time of 34 minutes, for a dive at 100 meters during 15 minutes with 12 of them on the bottom.

These first experimental dives were successful, however, they were not numerous enough to obtain definite conclusions. They were not numerous because helium is not readily available in Europe; its importation from the United States requires extensive complicated procedures and it is very expensive. We hope further study will indicate that we are correct.

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STUDIES OF DECOMPRESSION AND INERT GAS-OXYGEN MIXTURES IN THE U. S. NAVY

R. D. Workman
Commander, Medical Corps, U. S. Navy
Experimental Diving Unit
Washington, D. C.

Decompression studies in the U. S. Navy during the eight years since the First Underwater Physiology Symposium in 1955 have provided a repetitive air diving method with flexibility to permit as many as eight dives daily as deep as 190 feet with safety from decompression sickness[1]. Decompression schedules for exceptional exposures were developed to provide for 12 hour exposures through 140 feet and up to three hours at 300 feet[2].

Duffner has carried out helium elimination studies following 12 hour exposures at depths from 35 to 50 feet[3]. These were followed by determination of the minimal decompression exposure limits for helium dives at depths to 225 feet, thus permitting adaptation for use of helium-oxygen in mixed gas SCUBA[4]. The use of these mixtures was felt necessary due to occurrence of carbon dioxide retention in divers using nitrogen-oxygen mixtures with the resultant increased risk of oxygen toxicity[5]. Concomitant benefits of reduction in breathing resistance[6] and narcosis[7] permit the diver to perform his task at greater depths more effectively.

The projection of allowable tissue tensions of helium to provide adequate decompression has confirmed earlier impressions that somewhat deeper decompression stops are required than for nitrogen following the same depth time exposures[8]. A review of studies of bubble growth and resolution factors[9,10] reveals the relationships expressed in the following equation which may be meaningful as an explanation:

$$R^2 = R_o^2 + (sK/P)\ (ci - Cs)\ t$$

R_o = bubble radius at t = O

K = coefficient at diffusivity

P = density of gas in bubble

Ci = dissolved concentration of gas in solution

Cs = dissolved concentration of gas in solution at saturation

t = time in minutes.

Thus to compare relative growth of bubbles containing helium or nitrogen:

Factor	He	N_2
K	2.56	1
P	1	7

$$He_2/N_2 = 2 \times 2.56 \times 7 = 35.8/1$$

Therefore helium shows 35.8 times the propensity for bubble growth of nitrogen in a supersaturated solution in which the respective gases are at the same concentration. Though the solubility of nitrogen in oil is 4.5 times greater than helium, it is only 1.45 times greater in water than helium. Thus, the relative bubble growth rate for helium over nitrogen in a saturated aqueous solution would still be about 25 times greater.

The probability for bubbles of inert gas to form in supersaturated solutions and tissues has been expressed as follows[11]:

ΔP = T − H

T = sum of partial pressures of gas in solution

H = hydrostatic pressure plus surface tension of liquid and tissue turgor.

Therefore, initiation of bubble formation should be comparable for different inert gases in solution for the same values of T and H.

The rate of growth of the helium bubble, once initiated, would appear to be a factor requiring more accurate control of the decompression depth to prevent initial bubble formation. Upon starting air breathing on the surface following a helium dive, the greater effective gradient for helium elimination over that for nitrogen will reduce the time-course of tissue supersaturation as a factor in initiation and growth of bubbles. This is also important in reducing the decompression required for repetitive dives on helium since the initial tissue tension of gas at the beginning of the dive adds an obligation for decompression time[1].

A comparison of allowable tissue tensions of inert gas projected on the basis of constant differential pressure (ΔP) to that permitted by a constant ratio of tissue tension/ambient pressure is presented in Figure 1. It is apparent that a 1.7/1 ratio, as used for conventional helium decompression calculation, will permit safe decompression until it exceeds the value projected by constant ΔP. That use of this constant ratio was not permissible at greater depth was evident during tests of helium dives to 495 feet by occurrence of bends as deep as 130 feet[12].

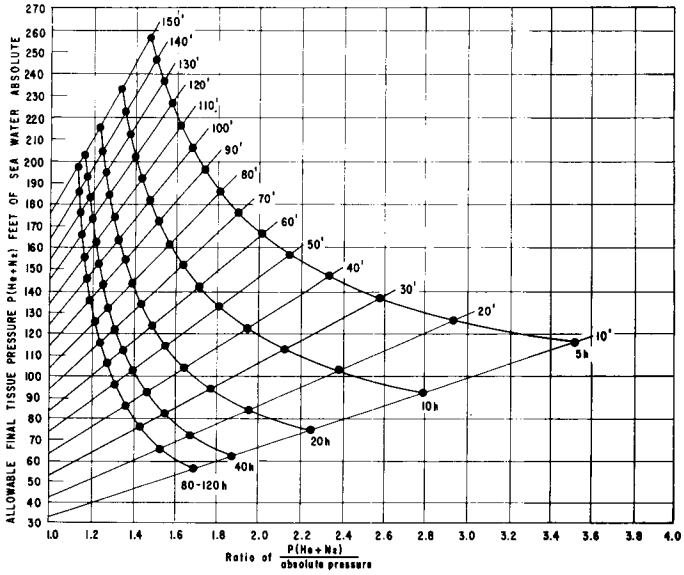

Figure 1. Allowable Final Tissue Pressure $P(He+N_2)$ for Helium-Oxygen Dives at the Various Decompression Depths Based on Constant ΔP

It is difficult to know what theoretical mechanism to prevent bubble formation would permit a constant increase of ΔP, which occurs with use of a constant ratio of gas tissue tension to ambient pressure (Figure 2). While somewhat deeper decompression stops are required for deeper dives when controlled by ΔP constant rather than 1.7/1 ratio, the total decompression time required will not increase appreciably, since the slower half-time tissues usually control only at the shallower depths.

At the present time, testing of repetitive dive schedules for use of helium-oxygen in mixed gas SCUBA is in progress at the Experimental Diving Unit (EDU).

The considerable advantage realized over air decompression is apparent in Figure 3. This is due to the greater efficiency for helium elimination from the tissues during the surface interval with a larger outward gradient than following an air dive.

Renewed interest has arisen at EDU in use of multiple inert mixtures as a means of exploring the differential gas solubilities during an exposure, to reduce decompression required over that where either helium-oxygen or nitrogen-oxygen mixtures are used. A review of Webster's article in the 1955 Proceedings of the Underwater Physiology Symposium[13] led us to consider it to be not particularly applicable and without a mechanism of action. Furthermore, use of helium-nitrogen-oxygen mixtures during the early exploration of use of helium in diving was reported unfavorably by the Royal Navy[14]. Nevertheless, it was considered that several hypothetical advantages to be derived from such mixtures should be tested. As a result, dives at depths of 100, 150 and 200 feet

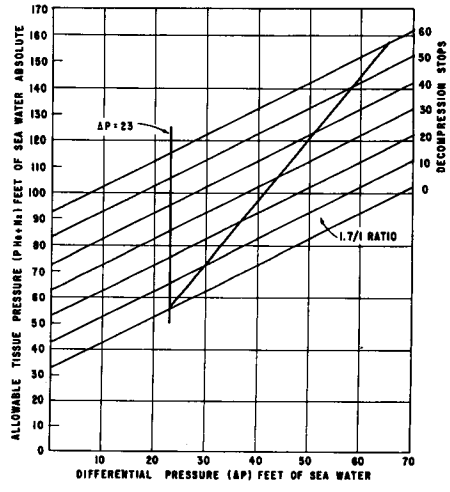

Figure 2. Allowable Tissue Pressure P $He+N_2$ of Control by 1.7/1 Ratio P $He+N_2$/abs pres compared to ΔP

with increasing exposure time were made to compare to decompression requirements for helium-oxygen mixtures at these depths. Figures 4, 5 and 6 show a graphical comparison of these decompression schedules to those for air and helium-oxygen mixtures when decompression was carried out on the same mixture used for the dive. The purpose of this series was to define the allowable inert gas tissue tensions at the decompression stops and upon surfacing. These values are found to be considerably in excess of those permitted with helium or nitrogen. While these values permit prediction of decompression schedules, the theoretical mechanisms of this advantage remain to be confirmed. Briefly, this is considered to be the differential partitioning of these inert gases due to their widely varying lipid solubilities in different anatomical sites, though represented by the same physiological half-time in terms of tissue perfusion and gas uptake capacity[15].

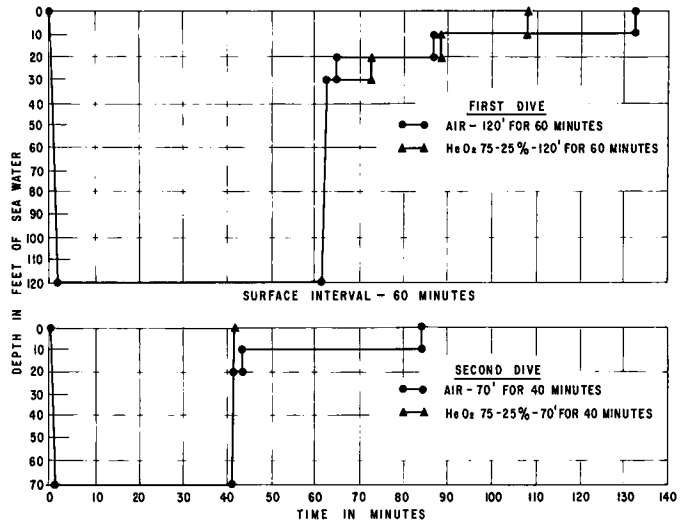

Figure 3. Comparison of Decompression Requirements for Air and 75-25% HeO_2 Repetitive Dives

This is an altogether too brief and sketchy statement of the attempts made by the U. S. Navy to provide decompression schedules for longer, deeper and repetitive dives required by operational units. Deep diving has had little priority in the U. S. Navy in recent years, but new operational requirements promise to make possible further projection and testing of theoretical concepts in this area, and the development of a deeper diving capability.

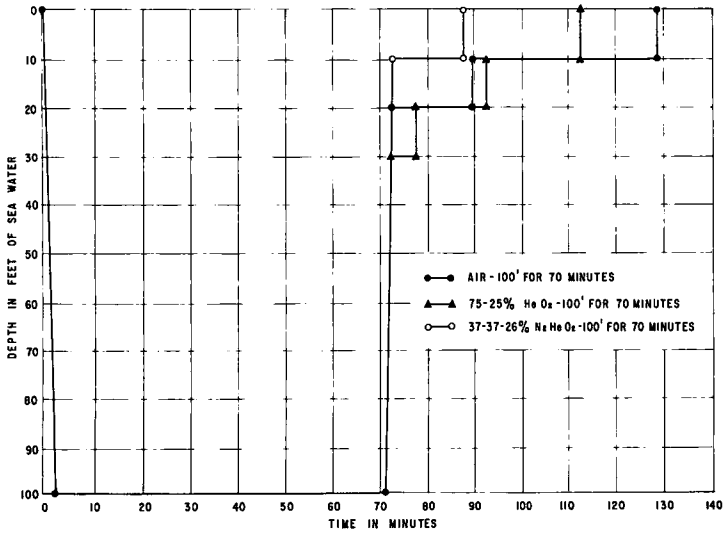

Figure 4. Comparison of Decompression Following Dives with Three Different Breathing Mixtures. 100 Feet

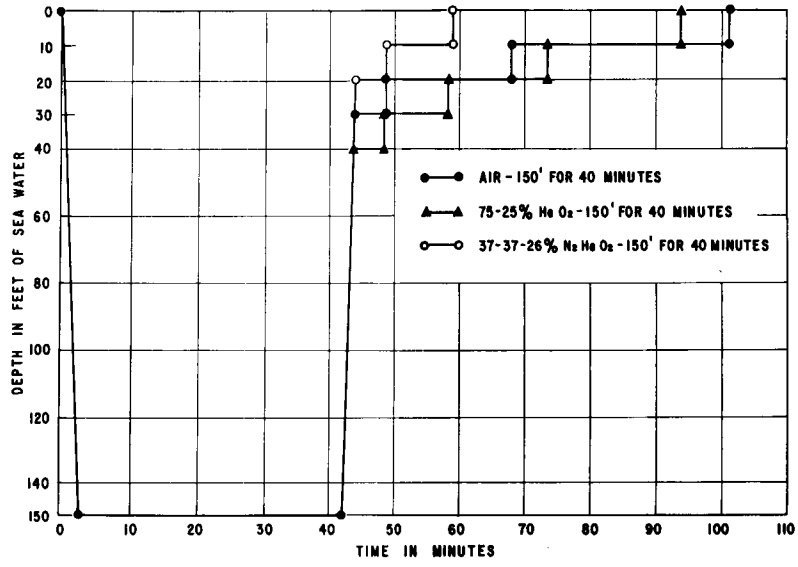

Figure 5. Comparison of Decompression Following Dives with Three Different Breathing Mixtures. 150 Feet

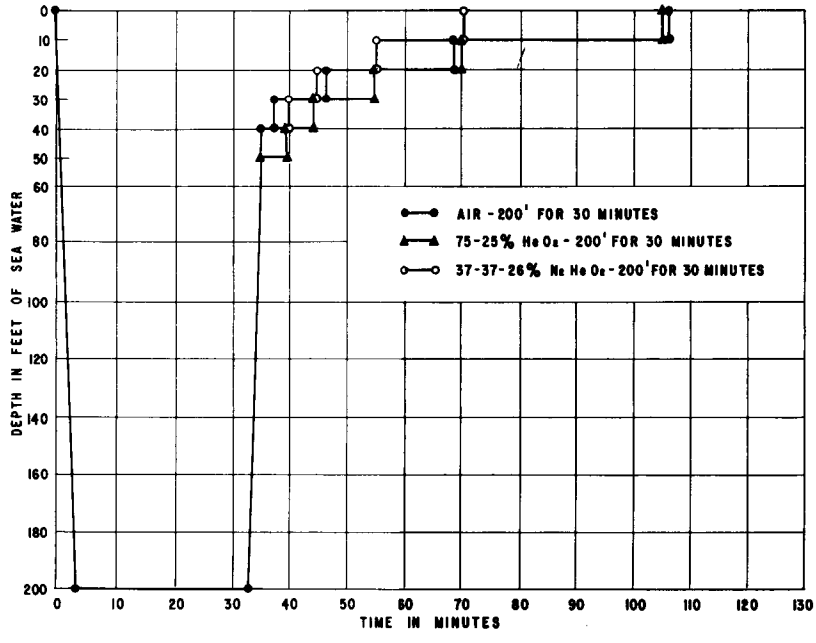

Figure 6. Comparison of Decompression Following Dives with Three Different Mixtures. 200 Feet

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PROLONGED EXPOSURE TO HIGH AMBIENT PRESSURE

G. F. Bond
Captain, Medical Corps, U.S. Navy
Naval Medical Research Laboratory
Groton, Connecticut

The purpose of this symposium is to extend and clarify man's ability better to utilize the products of the marine biosphere which covers nearly three-quarters of our earth. Within this salt-water environment is found a great portion of the protein requirement of our generation; the mineral, archeological and meteorologic discoveries of years to come; the possibility of fresh water recovery; a new generation of antibiotics for human use; and, finally, a new area for fundamental research, with intelligent exploitation of our findings. The reaches of space are a challenge to man's intellectual grasp; but knowledge of the ocean's environment, products and impact on civilization deserves serious and urgent attention of the world's scientists, if human survival is to be guaranteed.

Man's desire for personal conquest of all reaches of the sea has been an enduring dream, extending backward past the span of documented history. Since the early 14th century, laborious and hazardous steps have been recorded of human effort to return as a free-ranging, effective agent to the ocean depths from which we once emerged to become dry-land inhabitants. With considerable ingenuity, the capacity of man's undersea existence and function has been advanced through development of diving bells, submarines, deep-sea diving gear, SCUBA equipment, and lately, with unpressurized vehicles capable of reaching the ocean bottom at its greatest known depths.

Despite the technological developments noted, the capability of prolonged, free-ranging existence at depth remains, at this time, beyond man's reach. Encapsulated in pressure-proof submersibles, we are presently able to range for appreciable distances, both vertical and horizontal; from within these vessels, local and remote observations can be made, and samples of the environment secured with prosthetic devices. Yet this does not suffice. In order to absorb and utilize every facet of the undersea environment, it may be necessary that the investigator have complete freedom of movement, and an ability to coexist under conditions identical with those of the marine biosphere under scrutiny.

An approach to this freedom may be attained through use of conventional deep-sea diving equipment, or with self-contained underwater breathing apparatus (SCUBA). Operational limitations of these devices, however, must be recognized. Utilizing the older "hard-hat" diving suit, the diver is not only tied by an umbilical gas-line to the surface, but hopelessly limited to a tiny circumference of search and observation. With use of SCUBA gear, considerably greater individual range is permitted; yet the availability of self-transported gas is a limiting factor, quite serious at depths beyond 15 fathoms. More importantly, in either case the individual is subjected to immutable laws of physics, which would seem to limit

not only the duration of undersea exposure, but also the depths to which man, as a free agent, may be effective.

About six years ago, personnel of the Naval Medical Research Laboratory began to explore new approaches to the old problem of inner-space conquest. The reasons for this interest are apparent, from military and civilian point of view alike. For military purposes we sought the capability of undetected underwater existence and construction. On the other hand, this research, if successful, would certainly enhance scientific utilization of oceanic resources. At the time, it seemed a worthwhile goal; and we pursued it with enthusiasm.

At first, it appeared that two major problems were involved; the choice of respirable gas mixture at any depth; and the ultimate question of decompression. Initially, we sought to provide a respirable mixture which would minimize narcosis and breathing resistance alike; next, the problem of decompression after total body saturation required resolution. Since the operational concept would involve exposure of man to gas pressures of up to 20 atmospheres for infinite periods of time, a great deal of basic work remained to be done.

As a beginning, it was desirable to reconfirm the fact that compressed air would not be a satisfactory breathing medium for man under these conditions. Although this probability had been demonstrated by Drinker and his associates some three decades past[1], the experiments were repeated, with some extensions. We were soon able to show that compressed air, breathed at an equivalent sea depth of 200 feet, was lethal for selected wistar strain rat populations after 35 hours of continuous exposure[2]. Examining the hypothesis that increased partial pressures of oxygen caused death, we subjected equivalent groups of animals to an atmosphere in which the partial pressure of oxygen was held at 160 mm/Hg, with nitrogen gas making up the pressure differential to seven atmospheres. In this case, all but one of 16 animals survived a 14-day exposure, but specific and irreversible lung lesions were found in the case of all survivors of the experiments. These lesions were attributed in the main to the density of the breathing mixture, although consideration was given also to the narcotic effect of nitrogen at this depth, insofar as it might alter normal respiratory pattern[3].

A final check was made on the lethal effect of oxygen. Another matching rat group was exposed, under similar conditions of temperature and humidity, to an atmosphere of 100% oxygen, at a pressure of approximately 22 psi absolute. This exposure yielded an oxygen partial pressure of about 1120 mm/Hg, equal to that of the initial experiment at 200 feet (103 psi absolute), which had previously resulted in 100% mortality after 35 hours. In this experiment, with reduced gas density and with the element of nitrogen narcosis excluded from the design, we again reached 100% mortality in 35 hours of exposure. Data from these exposures convinced us of the predictable lethality of oxygen, with respect to our animal subjects[4].

Considering that the specific deadly effect of excessive exposure to high P_{O_2} had been demonstrated, our next effort was to reduce the density of the inert gas component. The obvious lighter inert gas of utility, of course, was helium.

In the U. S. Navy, helium and oxygen mixtures had been used for divers' breathing sources for some decades, covering many thousands of hours of intermittent human exposure. Nevertheless, many competent physiologists were convinced that atmospheric nitrogen was essential to mammalian existence. It was necessary to complete a number of experiments in which nitrogen was absent from the respirable atmosphere, to settle this point at an animal level. Following the neglected example of Barach[4], with sophistication of design parameters and a larger number of animal subjects, we exposed a rather large colony of rats to an atmosphere of 80% helium, 20% oxygen, for a period of 16 days, with no adverse physiological effects, immediate or delayed[2]. Thus, a long series of helium and oxygen exposures was commenced.

Starting with the original species choice, we extended animal experiments under high pressure to encompass four more species, including goats and squirrel monkeys. After two additional years of successful experimentation, we were able to report that all animals exposed to our selected mixture of helium, oxygen and lesser quantities of inert gases not only survived a 14-day exposure at a simulated depth of 200 feet, but could be safely returned to surface pressures with no physiological damage. Decompression problems, and treatment of decompression accidents involved in such an exposure, were clarified in a separate series of experiments[2]. The animal exposures were concluded.

In 1962, the Secretary of the Navy granted permission for utilization of human subjects in extension of this project. Shortly thereafter, following a cautious plan, the first set of volunteers was exposed to an essentially nitrogen-free atmosphere, for a total exposure of 144 hours. In this significant experiment, the average composition of the ambient atmosphere was 21.6% O_2, 4.0% N_2, 74.4% He. Three human volunteers were selected for the exposure. Choice was determined by age, pressure experience, and available physiological information. As in the case of our animal experiments, all parameters of blood chemistries and morphologies were carefully evaluated; in addition, EKG, EEG, metabolic values, and a multitude of psychophysiologic test values were obtained.

In this experiment, not yet published, all major goals were achieved, and the human subjects completed the exposure with no measurable physiological decrement. Incomplete analysis of the test results, however, indicate a clear-cut stress response, a potential bacteriological problem, and a persuasive suggestion that inert gases of man's respirable atmosphere may exert a specific physiologic effect on the exposed individual. There is scanty evidence that the sum total of these effects might be advantageous to the human organism. In short, it is believed possible that ocean air is not the best of all possible atmospheres for human existence.

From data derived in this experiment, we are encouraged to proceed to the next phase, requiring exposure at 100 feet of depth for a period in excess of six days. Following this, an exposure to 200 feet for a period of more than 14 days is planned. If information from these exposures is acceptable, it seems likely that man might tolerate habitation in pressurized circumstances up to and beyond 600 feet of ocean depth for an infinite period of time, with a decompression penalty of less than 4 days.

Assuming that we are successful in early human phases of our experimental project, it cannot be said that the problem is solved. Examination of available data indicates, among other things, that the thermodynamic properties of a pure $He-O_2$ mixture may prevent its use at high pressure, where increased molecular availability will multiply the heat transfer problem. Likewise, it seems certain that we should utilize a system of multiple inert gases, in the interest of shorter and safer decompression periods. Work along these lines commenced in 1957, is continuing at present, and shows considerable promise. Finally, a vast amount of basic data must be obtained from human and animal experiments, to validate early empiric findings.

It is our belief that a new and useful concept has been developed which will make feasible prolonged and free-ranging existence at depths to 100 fathoms. Once man has demonstrated a capability to survive undamaged in such an environment, the provision of suitable mobile and fixed habitations, together with all necessary equipment for underwater work and life, will follow very quickly indeed.

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FIRST SESSION
EXTENSION OF DIVING DEPTH AND DURATION

G. J. Duffner, Chairman

INTRODUCTION

Voltaire once said, "The discovery of what is true and the practice of that which is good are the two most important objects of philosophy." Similarly, the discovery of what is true and the practice of that which is safe are the two most important objectives of underwater physiology.

At the time of the last symposium needs were expressed for, among other things, repetitive diving tables, multi-level or depth exposure decompression tables, and mixed gas decompression tables. Need existed for new knowledge concerning the inert gas exchange in the human body upon which we could base more rational mathematical integrations of complex exposures to elevated atmospheric pressures. We are interested in learning more about man's adaptation to the underwater environment. In seeking our answers, however, we must be mindful of the way we formulate our questions.

Sir Isaac Newton said, "If I have made any valuable discoveries it has been owing more to patient attention than to any other talent." These next two days belong to the patient workers whose minds seek to illuminate the darkness of the unknown in underwater physiology. In all seriousness I can think of no more appropriate means of opening this session than to borrow a question from the Book of Isaiah, the 21st Chapter, the 11th Verse. "Watchman, what of the night?"

DISCUSSION

DUFFNER: Mr. Hempleman, in 1960 we discussed the matter of whether or not the rate of gas uptake was the same as the rate of elimination. Would you elaborate on this subject?

HEMPLEMAN: The problem is really rather complicated. If a man is decompressed and on his first decompression stop he is brought to a pressure which approximates his bends threshold, gas emboli may be present in him. Nevertheless, he may never have any manifestations of pain if he is not removed from the depth of that stop. During repetitive diving one may encounter tremendous problems. Is gas elimination the same as gas uptake? I think you have to select dives very carefully in order to demonstrate that bubbles are present. We often do multiple stop dives, don't use adequate deep stops, and then in the subsequent drops in pressure we steadily aggravate the situation created earlier in the decompression. We are, therefore, postulating longer and longer tissue half times to explain this, when really what we are doing is unnecessary therapy.

DUFFNER: As I recall, in the present Royal Navy tables, two different rates of gas exchange were used in table development. One was for uptake which

was essentially Rashbass' original equation[1], and then a slower one, which was called the bubble regression curve.

HEMPLEMAN: Rashbass' table was based on a Δ_p concept, as opposed to ratio, and when it was actually tested it was found not be be based upon a true hypothesis.

DUFFNER: Did you mean that you now believe that bubbles actually do not occur in the tissues? You said that the only way a bubble could grow was for it to end up in a tissue or the blood stream where there was a rich gas supply. Do you think that all of the gas present in the tissues is in solution or does some of it form bubbles too?

HEMPLEMAN: We have observed men after helium-oxygen diving who have had mild attacks of the bends. They will complain of a pain in the shoulder which is transient and which may last about ten minutes. It may shift to the left knee later on, having gone a long way in a short time. We also have observed in our goats that the appearance of bends was entirely random from the left to the right side of the animals. In tunnel workers, when the men had multiple bends, practically the same number had pain in the left knee as in the right knee and a lot have pain in both knees. You must postulate some central mechanism which switches from one side of the body to another, or some factor that is common to both sides of the body. The only thing that occurred to me was the blood flow which is common to both sides of the body. Work has been done on the relationship between susceptibility to bends and the surface tension of blood, and it did seem that the blood was the likeliest source of the initial trouble, but the bubble can't grow unless it reaches some reservoir where it is fed with gas.

DUFFNER: Dr. Besse, I would like to hear more about your experience with the helium-oxygen mixtures in the DC55. In the U. S. Navy there was an initial reluctance to use helium in SCUBA diving because many say that bends incidence is increased. Could you tell us about bends incidence in your experience with helium-oxygen mixtures in the DC55?

BESSE: We have never had bends with the DC55.

DUFFNER: What exposures have you used in getting some of the depth-time values?

BESSE: We used the apparatus for nitrogen-oxygen mixtures as well as for helium-oxygen. Our calculations for decompression were made for the mixtures used. A dive to 100 meters with helium-oxygen is begun breathing a mixture of 50 per cent oxygen and 50 per cent helium. At 30 meters the mixture is changed to 10 per cent oxygen and 90 per cent helium. The bottom is reached in three minutes, and an additional 12 minutes is spent at 100 meters. Ascent is made at a rate of 20 meters per minute. When arriving at 30 meters we change back to 50-50 HeO_2. A one minute stop is taken to change the mixture, to change the bottle, to open the bottles and to arrange the apparatus. We stop for one minute at 15 meters to switch the mixture to pure oxygen. The decompression stops from there are: one minute at 12 meters, five minutes at nine meters, eight minutes at six meters and 13 minutes at three meters. About six such dives have been made.

BOND: How does that compare with our decompression?

WORKMAN: It is somewhat shorter. We have calculated the tissue tensions at the various stops. Of course, the approach is one of oxygen decompression. The slides I showed related to use of one mixture throughout the decompression, which permits us to make a direct comparison of time for various mixtures. It is obvious that our 200 foot dive at 30 minutes was quite in excess of the decompression time described by Dr. Besse.

BESSE: Sometimes we have used nitrogen-oxygen mixtures between 30 and 15 meters, but there is no change in decompression time.

WORKMAN: However, the dives you described were at rest in the chamber, I believe. They are not swimming or work dives in water.

BESSE: No, they were in a dry chamber.

WORKMAN: This is important. One would expect a maximum or an increased decompression requirement for hard working dives compared to rest dives. Perhaps this is sufficient explanation for the differences.

DUFFNER: It is worth considering the virtue, after switching to oxygen, of continuing progressive ascent while decompressing on oxygen as opposed to stepwise ascent.

BEHNKE: I am surprised that so few measurements have been made of gas elimination. I have a slide of some old experiments with Willmon[10]. The experiments all involved an exposure of 75 minutes at 100 feet with different subsequent stops. The purpose was to ascertain whether the blood could hold an inert gas in supersaturation — a very fundamental question. The procedure was to measure the elimination of nitrogen at different levels. The first level was at 100 feet, breathing pure oxygen for a period of 27 minutes. Another level was 50 feet breathing pure oxygen for the same period of time. The third level was 20 feet. In other words, in the last experiment one went abruptly from 100 feet to 20 feet. The thought was that if bubbles actually formed, perhaps there would be a retardation in the amount of nitrogen eliminated. We expected to see the greatest amount of nitrogen eliminated when oxygen was breathed at 100 feet, (at the level of original exposure to air), and decreasing amounts of nitrogen eliminated as the depth of O_2 breathing was decreased. We found the amounts of gas eliminated at 100 feet breathing pure oxygen to be the same as the amounts of gas eliminated after an abrupt ascent to 20 feet. I show this slide to indicate the need for more gas measurements. It is really quite amazing to me that they have not been made. Captain Duffner[2] has employed a fine procedure by putting individuals in a low pressure chamber several hours after decompression to get an estimate of whether or not bubbles were still present. However, the chance that bends may occur is really such an unreliable way of estimating what is going on inside the body that we must get back to gas measurements.

DUFFNER: I agree with you wholeheartedly. It is almost a tragedy that some of the early work of Hardin Jones, Smith and Morales[3,4], using radioactive gases to study inert gas exchange, was limited by counting ability to measurements

of only a hand or an arm. Now that we have total body counters and scanners, we could find out whether or not the gas is there, how much is there, and where it is. Yet nobody seems to want to do this. We have these measurement facilities available and yet everybody wants to construct mathematical expressions and try them, without any further experimentation.

I detected a difference of opinion this morning whether it was permissible to use a constant ratio in decompressing. The U. S. Navy position, expressed by Commander Workman, was that you had to change the ratio with the depth. I gather that Mr. Hempleman, and perhaps Lieutenant Besse, felt that this was not the case. Did I misunderstand?

HEMPLEMAN: I think that you can do very well with what you might call "rapid dives." They look very spectacular, but when they fail they tend to fail spectacularly. This has made us terribly cautious, after trials of minimal decompression.

DUFFNER: Dr. Workman, how did you determine the adequacy of the decompression required in your studies?

WORKMAN: It was entirely on the basis of the symptoms of the bends. This, of course, does not give you quantitative information on how safe or how unsafe the dives may be. Ideally, to test such a thing, a large group of subjects is required and we can't do it with the number of subjects we have. We realize very well that there is individual variation in bends susceptibility of a particular schedule. In our group we very probably assess a considerable sample of the divers we have in the Navy. In quantitative methods that one might apply (the altitude technique which has been mentioned) may, in certain situations, have some value. I think that there are problems in applying it with helium. We were reluctant to use it in the helium-oxygen decompression studies, in that a marked individual variation was recorded in a series of ten dives in which the altitude technique was used. Some divers bend on the surface without going to altitude. There was a work period associated with the surface interval. Some bent on going to altitude and some went the full 60 minutes at altitude during which graded exercise was performed. Unfortunately, there were instances in which bends treatment was required. Four men who came back to atmospheric pressure after altitude required subsequent treatment. The very wide individual difference on this dive of only about 90 feet for 30 minutes on helium-oxygen (80-20 He_2-O_2 mixture, I believe) didn't give us much confidence that altitude exposure was an assessment tool for helium diving. The altitude used was 18,000 feet and one perhaps might modify this and use some shallower depth. The implication is that altitude as a measuring tool will require a tremendous amount of use to determine its validity and reliability. It was not very reproducible.

Further exploration of the altitude technique was made with longer dives on air. The initial work was done on a series of 30 minute exposures at increasing depths (90, 110 and 125 feet) and it appeared possible to assess a difference between these exposures that was statistically meaningful. However, longer exposures, which would perhaps be stressing to the more slowly perfused tissues did not give very reproducible results on going to 18,000 feet.

I think that the slide Dr. Hempleman showed of the 30 foot difference range of susceptibility for goats was quite constant throughout the depth-time exposure and is meaningful. However, I think that in bends studies, work is usually done in terms of the least common denominator. Dr. Hempleman has shown that this was not a constant at various depths. Some animals are exceedingly resistant to decompression sickness for deep brief exposures and yet for medium depth and shallow depth exposures they varied within this span of susceptibility. Therefore, to quantitate bends it would only be meaningful, as far as symptomatology is concerned, to make comparisons at one depth-time exposure. That finding cannot necessarily be related to another time exposure. This leads us to suspect our ability to quantitate throughout this diving range with the altitude or other techniques.

DUFFNER: One of the problems in comparing decompression procedures is that you can never prove the hypothesis of "no difference," because this takes an infinite number of experiments. In an attempt to get around this problem and to dissect the decompression process into its elements and study them, we at the Experimental Diving Unit worked out the altitude technique. We exposed men to 125, 110 and 90 feet for 30 minutes. They swam against an eight pound pull on the ergometer. Following this they were decompressed to sea level at a rate of 60 feet a minute. After 45 minutes (some mild exercise was done in the last 30 minutes) they were taken to 18,000 feet of altitude, half an atmosphere. They stopped at 10,000 feet to change to breathing pure oxygen. Once they got to 18,000 feet altitude they again began to do mild exercise. They were kept at altitude for an hour. We found that of the men who were exposed to 90 feet for 30 minutes, two developed no symptoms, while eight had symptoms near the end of the exposure. Those who had been exposed to 110 feet had symptoms in the middle range of the exposure to altitude. The most severe symptoms were recorded following exposure to the 125 foot depth. The symptoms were experienced either on the way to the 18,000 foot altitude or immediately after getting there. The temporal occurrence of decompression sickness was a feature of this technique.

This worked out quite well for thirty minutes of air breathing. Commander Workman pointed out that when it was tried on helium-oxygen it proved to be unpredictable. This may be a productive research area, but it certainly requires more work.

DUFFNER: Captain Bond, when you exposed animals to pressure for long periods in the nitrogen-oxygen atmosphere, you said you thought the nitrogen contributed to the development of symptoms[5]. Do you have any evidence that the density of the respiratory mixture was a factor? If you had a diminished alveolar ventilation you should develop a respiratory acidosis. This should in time become partially compensated but could still lead to deterioration. Now do you have any evidence that the animals which were exposed to the 3 per cent oxygen 97 per cent nitrogen did have an acidosis?

BOND: We have no such evidence. We did our studies on the animals immediately after they were brought out and at varying intervals thereafter. Chlorides, potassiums and CO_2 measurements were within normal limits. I might point out though that, in my opinion, the quantity of lung tissue involved in these cases was possibly not sufficient to give the results that you would predict

and I would further predict that on perhaps the third day of exposure when pulmonary damage, due to oxygen irritation might be expected, I suspect that at that time we did have an acidotic condition. We did not choose to go into the chamber and interfere with the animals and so we don't have complete values.

DUFFNER: I think that whether man can maintain an adequate alveolar ventilation is a critical question. As for decompression, we have Mr. Link in the audience. Mr. Link, what was the first decompression stop for Stenuit's prolonged dive on helium-oxygen at 200 feet?

LINK: I haven't the figures right here but have them in print[6], so they are available.

DUFFNER: Dr. Bornmann was there. What was the first stop?

BORNMANN: The first stop was 120 feet. We kept Stenuit for 15 hours between 120 and 100 feet. We then brought him up to 53 feet and he developed pain. So we took him back to 70 feet and kept him there for 12 hours before proceeding with further decompression.

DUFFNER: What was the length of the dive?

BORNMANN: Twenty-four to twenty-six hours. It was actually about 24 hours at 200 feet. Bottom time was 26 hours.

DUFFNER: Twenty-four hours at 200 feet. The breathing mixture was about 95 to 97 per cent helium. Although Dr. Bornmann said the first stop was 120 feet, this man went on to get decompression sickness at 50 feet. Mr. Hempleman said earlier that we sometimes treat things we have caused further down. So I would say, Captain Bond, that you would be well advised not to make the first stop at 84 feet after such a dive.

BOND: I think I indicated that, Captain Duffner. However, I would emphasize that the subject was at 100-120 feet for approximately 15 hours. This would lead me to the conclusion, not that the initial bends occurred at the 120 foot stop, but that a critical tissue ratio was exceeded in going from 120 to 50 feet. I do not think that was wise.

WORKMAN: The ratio as calculated was about a 1.45 to 1 ratio for helium over the ambient pressure. This is regarded by some as evidence for the necessity of reducing helium ratios at depth. On the plot of the Δ_p for the 120 minute tissue, this is predictable. It exceeds slightly what would be permissible at this depth on a Δ_p reduction.

BOND: Mr. Hempleman would you comment on the subject of decompression of an almost totally avascular tissue, viz., the crystalline lens of the eye? We are faced with totally saturating human organisms for long periods of time and must assume that by diffusion the crystalline lens, which is considerably thicker than one millimeter, will become saturated. We are afraid that this might be a completely limiting tissue of the human body, since it has no blood supply. Would you care to comment?

HEMPLEMAN: Actually the lens is one of the avascular structures we have thought about in considering diffusion versus perfusion situations, but I'm afraid that I've always dismissed it. I've never really considered it from the point of view of its being a source of trouble.

BOND: We did not find any evidence of bubbles or damage in the crystalline lens in any of our animals using the best techniques that we had. Long bone x-rays were likewise done and we found no cortical destruction. I am still at a loss to explain the fairly rapid diffusion rate in an organ such as a crystalline lens. The cornea is no problem. It derives its oxygen from ambient air and naturally has a high diffusion rate.

HEMPLEMAN: I did want to state that I thought that the bubbles really were lodged in fairly vascular tissue, not in avascular tissues. I was forced to that conclusion by the oxygen experiment I described.

BOND: Dr. Workman, you pointed out the beautiful efficiency, at least in a few runs, of using a multiple inert gas system of helium-nitrogen-oxygen. Would you care to comment on the possible desirability of a five inert gas system for diving?

WORKMAN: I think there are some basic studies that are required to define this approach. The fact that most of the other inert gases that one might use have somewhat greater solubility coefficients than nitrogen or helium may somewhat limit the increased value that one might derive from them. The other factor, of course, is that the other gases one might use, such as argon and neon, have rather high molecular weight and would probably increase the breathing resistance appreciably. It is desirable to keep the breathing resistance as low as possible and, of course, helium is about the only gas that helps much for that. I am personally not very much inclined to consider hydrogen as safe in this situation. The operational complexities of the use of hydrogen outweigh any advantages. I would prefer to use nitrogen and helium, the two inert gases which are commonly used, and about which we have considerable information.

The mechanism that we foresee giving this advantage, a differential solubility and different anatomical sites that may be presented by the same physiological half-time, would not seem to gain a similar advantage from using mixtures of argon and nitrogen or argon and helium.

HEMPLEMAN: We have been doing argon saturation dives and helium saturation dives on goats and there is no doubt that the goats are worse off diving on argon-oxygen mixtures than on nitrogen-oxygen mixtures. Also they are worse off on nitrogen-oxygen mixtures than with helium-oxygen on saturation dives. When you start to move down in depth, the time scale of the difference gets shorter. If you assume that bends development following saturation dives is in some way dependent on the size of bubbles, then it is very convenient to assume that you have a certain number of molecules that form a bubble of a certain size.

DUFFNER: What is the ratio between the oil and water solubility of argon?

WORKMAN: About 5.6 to 1. It is about twice as soluble as nitrogen in fat, anyway.

DUFFNER: The reason I ask this question is that, from the standpoint of a radioactive gas, argon would be the easiest one to use because it has a high capture cross-section for thermal neutrons and it is very easy to make argon radioactive.

MACKAY (S): Much of the discussion has emphasized a fundamental need in supersaturation and bubble formation experiments for a definite indication of end point, and there may be a new approach. It is the use of ultrasound to detect the presence of tiny bubbles and the onset of the bends. In our laboratory at Berkeley, we have built pulsed 15-megacycle sound echo-exploring equipment, and gas bubbles are excellent reflectors. At this frequency, the wavelength is 100 microns, and these circuits can detect and follow the progress of single bubbles that are an appreciable fraction of this dimension, or larger. In the preliminary experiment, I demonstrated the change in properties (increased opacity) to ultrasound that rat tissue undergoes upon being given vigorous decompression sickness. A focused transducer and simple scan were used, but a bulk observation with continuous sound also should have been effective. Either sound transmission or back-scattering methods could be employed, and they would seem to provide an excellent tool both for in vivo and in vitro studies of the kinetics of bubble formation, for example with mixed inert gases. Some workers speak of "silent bubbles" and these should be detectable, if real. It might be mentioned that the sound intensities here are very low (about 0.001 watt/cm^2). Rapid excess inward diffusion of gas on a rarefaction half-cycle might allow intense sound to "pump up" otherwise unnoticeable small bubbles, in a fixed way, until detectable. I would imagine that a diver who was decompressing, and was hit by an intense sonar beam, might be given a case of the bends. We could investigate the effect of intense ultrasonic energy on a tissue having an over-pressure with our other therapeutic equipment, but I have not yet done this; degree of supersaturation might thus be measured.

LAMBERTSEN: There has been important discussion on the possible advantages to decompression of using more than one inert gas simultaneously in a breathing mixture for diving. However, there are also possible advantages in changing from one inert gas to another during diving or decompression. Could we have discussion regarding the theoretical considerations involved in repeated alteration of such mixtures as nitrogen-oxygen and helium-oxygen in the course of a pressure exposure? This has been a chronic question in my mind.

BRADNER: If the solubility and time constants of the gas are the same, then you do not gain in the decompression; if either one is different then there is the possibility of gaining by shifting from one gas to another. (Bradner & Mackay, Bull. Math. Biophysics 25, pp 251-272, 1963).

HEMPLEMAN: We have shifted to air during decompression stops following helium-oxygen diving. However, when we got bends that way it was often very severe, stable and difficult to treat.

DUFFNER: Within limits, it is not logical to attach significance to the seriousness of the case of bends. Of course, if a diver comes down with the chokes or arterial bubbling you can say that he had a grossly inadequate decom-

pression. However, I don't think that you can consider neurological symptoms to represent less adequate decompression than simple bends pain in the knee. Moreover, adequacy of decompression is also not clearly related to the pressure required to relieve pain during treatments (e.g., 165 feet as opposed to 60 feet). The diver who has neurological symptoms is a much more seriously ill patient than the man who just has a pain in his deltoid, but I don't think you can say he was less adequately decompressed. Dr. Behnke, in the helium-oxygen diving experiments, didn't you attempt to decompress on air?

BEHNKE: Yes. We hoped that on decompression, beginning with the first stop, it would be possible to substitute air and that the elimination of helium from the body would be as rapid breathing air as it would be breathing oxygen. Actually it was done routinely, and then we shifted to oxygen.

I now want to comment regarding the different situation in evaluating decompression for short versus long dives. We have had bends at 180 feet after brief dives to 500 feet. After a dive to 300 feet on helium-oxygen, coming up rapidly and making the measurements of the helium elimination from the body, we were impressed that the amount of gas eliminated in the first two or three minutes was far more than the pressure multiple would indicate. Therefore the diffusion factor was a problem with helium. On the other hand, in long exposures such as 12 hours at 90 feet on helium-oxygen mixtures, only 150 minutes of decompression was required in contrast with 12 hours decompression after diving. Finally I want to emphasize that use of short exposures to determine adequacy of decompression ratios are meaningless. It is necessary in ratio studies to use saturation dives and to have the gas pressure in the body in equilibrium with the gas pressure in the lungs. Has anyone in England exposed individuals to deep depths for 12 hours and then brought them out by any kind of constant decompression ratio?

DUFFNER: The only work that I know of is what Van Der Aue[7] did at the Experimental Diving Unit. He found that when divers were pressurized at 99 feet for 12 hours and then brought to 33 feet and kept there for as long as 24 hours, some still got the bends. So a two to one ratio just doesn't work in these circumstances.

HEMPLEMAN: We have also found this in animals.

VAN DER AUE: We exposed one group of eight men to 100 feet for 12 hours and then we decompressed them to 33 feet for 12 hours, and another group to 33 feet for 24 hours. A two to one ratio was used throughout, and of the eight divers we got two bends that required recompression. However, six of them did not get bends, so we were close to the border line. I found out later that the two divers who got bends had had a rough night the night before and were in no condition to act as subjects for the dive. Whether this had anything to do with the results, I don't know.

BEAN: In commercial work such as tunneling it has been quite a problem to finance these undertakings. The cost of insurance is increasing so much that tunneling operations may come to an end. I would like to have comment on the question of bone necrosis, a condition affecting the insurance costs.

DUFFNER: In the United States we have never been able to get good data on the incidence of bone necrosis. The only chance we had was on the third tube of the Lincoln Tunnel. We wanted to x-ray these people prior to employment but their union would not agree. However, Mr. Hempleman and a group in England were able to get some very good data on this topic.

HEMPLEMAN: X-ray examination of tunnel workers were made[8]. The majority of cases of definite bone changes occurred in the shaft and were non-symptomatic. The other cases were affected in the articular surface of the bone. On this basis it would appear that there is a definite incidence of bone necrosis in compressed air during a prolonged job. However, our compressed air workers do a much more savage type of routine than U.S. workers, they work eight hours in pressures up to 40 pounds per square inch every day for a week. After the men work eight hours, the decompression is essentially a Haldane type of decompression based on 5, 10, 20, 40 and 75 minute half-time tissues and a two to one ratio. My own preference is for a more conservative type of decompression than this, but unfortunately we don't have any data yet. The other thing that emerged was that some of the people with bone changes, alarmingly enough, had never had an attack of acute decompression sickness, so you apparently do not need to have an acute attack of decompression sickness with obvious bubbles in order to provoke this.

LAMBERTSEN: One of the difficulties to be considered in safely doing research on bends is tissue damage produced by an attack of bends. Bends is not just pain or paralysis, it may involve tissue damage or even destruction. Moreover, treatment is difficult. Will one of the Panel comment upon the possibility of employing saturation exposures to various gases here at sea level and studying the saturated individuals by the production of altitude bends. Would this not provide a screening procedure which would provide more information faster and more safely. Return to sea level would relieve most of the cases of bends which developed. Would you elaborate upon this? It might provide a means of study on a broader front.

DUFFNER: I do not think the two situations are exactly comparable. I'm not so sure that it is less hazardous. There have been a number of people who have died or been very ill with altitude bends. We recently heard about one who had been paralyzed for a week. Decompression to high altitudes is not a safe procedure. I feel that there is really no great danger in high pressure decompression. Under good conditions, as at the Experimental Diving Unit, I don't see any reason to depart from experiments involving positive pressure exposures.

WORKMAN: Dr. Balke[9] in 1954 did a series of altitude runs, attempting to relate nitrogen elimination to oxygen breathing and to exercise during altitude exposures at 38,000 feet. The quantity of gas eliminated did not correlate well with the incidence of bends at altitude. They found that it required two hours of pre-oxygenation at rest at atmospheric pressure to reduce bends incidence at altitude. About an hour of oxygen breathing during exercise at atmospheric pressure was needed to show reduction in bends incidence. The total quantities of nitrogen eliminated in many instances did not statistically relate to the freedom of bends at altitude.

LAMBERTSEN: This is not surprising, as all of us know, since it is the nitrogen which doesn't come out that produces symptoms.

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BLOOD COAGULATION AND CHEMISTRY DURING EXPERIMENTAL DIVES AND THE TREATMENT OF DIVING ACCIDENTS WITH HEPARIN

L. Barthelemy
Groupe D'Etudes et de Recherches
Sous-Marines (GERS), French Navy
Arsenal, Toulon, France

During 1962 the Underwater Study and Research Unit (GERS) studied certain variations in human physiology under hyperbaric pressure. These experiments were conducted together with some as yet unpublished experiments on animals, relating to survival, gas mixtures, and blood pH. We are dealing here with variations of some blood constants, especially coagulation during simulated dives and under the following conditions: compression, exposure to hyperbaric pressure and decompression. In this presentation we will examine successively blood coagulation during the dive, the use of heparin in the treatment of diving accidents, and changes in some blood factors.

BLOOD COAGULATION

In 1933 Aggazzotti[1], at the University of Modena, Italy studied coagulation times in animals (dog and rabbit) before and during decompression after exposures to pressures varying from 6 to 11 atmospheres. He found a shortening in coagulation time in most of the cases (12 out of 17) and an increase in coagulation time in 4 out of 17 animals. The increase in coagulation time seemed to occur in sick animals or those showing symptoms of decompression sickness.

In 1958 the French investigators Jullien, Leandri and Crozat (Marseille)[2], did some research which was partly resumed by Sautet, Jullien and Leandri[3]. They experimented on animals and man using the heparin test on animals and thromboelastography on man (2 cases). They found blood disturbances, the most important being a tendency toward increased coagulation shown by the heparin test and the thromboelastogram which appears in both animals and man when decompression is too rapid after exposure to hyperbaric pressure. These disturbances occur very early and are seen as atmospheric pressure is reached. While they even happen without any symptoms being perceptible they can be considered a pathological sign because, when rules of ascent are respected, no such phenomena are seen. Neither anesthesia nor intracardiac puncture and subsequent shock had any effect on these blood tests. All control animals were normal. When there was an increase of CO_2 in the breathing mixture, the blood disturbances observed were more prominent.

GERS has studied blood coagulation since 1959 and experimented on man and animals.

Experiments on man. Unpublished observations were first made at sea during actual dives on 15 divers, 20 to 35 years old (mean 28). Coagulation times were checked on slides after ten minute dives at 45 meters and were found to be shortened in 13 cases and increased in two cases.

Since this technique of performing coagulation time on slides is not quite accurate due to effects of thermal variation, the experiments were continued at GERS in the pressure chamber during simulated dives on the same divers as in the previous experiments. In this second series Duke's test[4] and coagulation times using the heparin method were employed. Samples were taken before, during and after the simulated dives.

Two types of dives were considered: 120 minute tissues with a supersaturation coefficient of 1.5 and 120 minute tissues with a supersaturation coefficient of1.8. The results appear in Table I. During tests with the 1.5 supersaturation coefficient, no modification of Duke's test was noted. The tendency to increased coagulation during stay under hyperbaric pressure is evident from the table. A decrease in coagulation time after return to atmospheric pressure cannot be considered as significant because the means of about 12 minutes are very close to each other and eight divers showed a shortening and six an inverse variation.

TABLE I

Description of Dives		Duke's test (mean)	Coagulation time (mean)
120 minutes 1.5 supersaturation coefficient	Before		12 min 40 sec
	During		10 min 40 sec
	After		12 min
120 minutes 1.8 supersaturation coefficient	Before	2 min	14 min
	During	2 min 40 sec	10 min 45 sec
	After	2 min 10 sec	11 min 30 sec

During dives with the 1.8 coefficient, the same procedures of sampling and measuring and the same experimental divers were used. An important shortening of coagulation time is again noticeable, especially during stays under hyperbaric pressures.

These experiments emphasized the occurrence of a shortening of coagulation time during stay under hyperbaric pressure, but decompression, especially when it was relatively slow, allowed recovery from coagulation disturbances. On the other hand, these disturbances persisted or increased when maximum allowable ascent speed was reached.

Our first findings seem different from the conclusions drawn by Jullien[2].

We have found that coagulation disturbances do not seem to be due only to decompression. Coagulation disturbances also appear during the stay under hyperbaric pressure. They improve, persist or even increase according to a more or less rapid or pathogenic decompression. Modifications of coagulation time seem to bear a relationship to other physiological modifications which appear during stays under hyperbaric pressure (CO_2 retention, pH decrease). However, we did not go into detail about these relationships.

Experiments on animals. Unpublished observations were made at GERS in order to explain the findings in man. Mice, rats and rabbits were used. These experiments showed that: coagulation time is not modified after return to surface when decompression is very slow, but is shortened when decompression is very rapid; coagulation time is very much shortened when breathing mixtures with a high Po_2 (compared to control animals whose Po_2 was kept at 0.20 atmospheres); coagulation time is shortened (but less than in the previous case) when breathing mixtures with a CO_2 content of 4 per cent at 6 atmospheres are used, and is also shortened when breathing mixtures with inert gas such as argon (due to CO_2 or inert gas only?) are used.

Recent research. In order to make these findings more precise, we have made at GERS more accurate experiments, using the thromboelastographic method[5]. Our aim was to emphasize whether hypercoagulability occurs in diving, and if it does, to determine its value, its origin (by coagulation diagrams), its etiology and the importance of its variations in relation to different pressures. The experimental divers were from GERS, 21 to 35 years old (mean 27). Samples of blood were drawn before the dive, during their stay under pressure, and ten minutes after return to atmospheric pressure. We studied the following thromboelastographic values with the results in Table II:

r	time of latency, thrombokinase time which has an average value of 13 to 17 mm
k	time of clot formation, thrombin time which has an average value of 7 to 9 mm
r+k	heparin test equivalent
am	maximum amplitude elasticity which depends on blood platelet function, fibrinogen rate and serum factors. Average value is 55 to 62 mm
am/r+k)	ratio which indicates a hypercoagulability when higher than 3 and a hypocoagulability when smaller than 2

In the 60 meter dive a tendency to hypocoagulability was recorded at every stage. In the 30 meter dive the (r+k) factor does not change but am (blood platelet fibrinogen factor) increases evenly. The am/(r+k) ratio shows a slight tendency to hypercoagulability.

These experiments show a slight tendency to hypercoagulability during dives of 30 minutes at 30 meters, whereas we find a hypocoagulability during

TABLE II

	r (mm) Mean ± SD	k (mm) Mean ± SD	am (mm) Mean	r+k Mean ± SD	am/(r+k) Mean ± SD
		12 minutes at 60 meters			
Before	14.1 4.5	8.75 3.1	57.55	22.7 6	2.80 1
During	16.0 4.2	10.6 2.7	56.45	25.1 7	2.50 1
After	17.1 2.8	10.5 2.8	56.75	28.0 1.8	2.20 0.85
		30 minutes at 30 meters			
Before	13.7	10.7	48	24.4	1.97
During	13	11.6	50	24.6	2.05
After	14.4	9.5	52	24.0	2.17

simulated dives of 12 minutes at 60 meters. In case of a hypercoagulation, blood platelets and fibrinogen levels increase, whereas thrombokinase and thrombin levels are subjected to small modifications. It will be necessary to pinpoint these studies in order to determine whether the hypercoagulability is actually due to the stay under hyperbaric pressure as indicated by our previous experiments.

As a matter of fact, it seems that the organism needs a certain time to modify its state and that a 30 minute stay at 30 meters is more stressful than a 12 minute stay at 60 meters (this fact appears in many of our measurements: arterial pressure, reaction time, Donnacio's obstacle). Apparently, a ten minute stay under 7 atmospheres pressure is not sufficient to obtain a new stable state in the organism and our measurements prove that the organism tries to adapt itself. We have noticed these facts in various experiments.

Our previous statements do not prevent strict use of decompression tables, since tables deal with physical decompression phenomena when our experiments seem to prove biological changes due to hyperbaric exposures where pressure is the stressful factor. Worth noting is the work of the Italian investigators, Lalli and Poggi (1962)[6] which emphasizes a shortening of Howell's time and thromboelastographic changes in relation to the tendency for thrombus formation after explosive decompression in rabbits.

USE OF HEPARIN IN THE TREATMENT OF DIVING ACCIDENTS

In order to improve the treatment of diving accidents, decompression sickness and air embolism in recompression, GERS had modified the classic tables of

the U.S. Navy and offered some adjuvant therapies such as heparin injections. From the following assumptions it appeared logical to treat decompression sickness by a quick acting, short term, anticoagulant such as heparin. Pathogenic decompressions are followed by a tendency to hypercoagulability and prolonged stays under hyperbaric pressures are also conducive to hypercoagulability. In case of an accident, bubbles produce tissue and vascular injuries and a clumping of blood platelets. A hypercoagulability should also occur in this case. However, as heparin may produce hemorrhagic accidents, we began with experiments on rabbits in order to study more specifically heparin action and its safe use in decompression sickness. A heparin dose of 5 mg per rabbit was selected. With this dose, heparin affects plasma clarification and has a scattering and vasodilator effect without increase in the coagulation time. Application to human therapy was undertaken later.

Experiments on animals (rabbits) (Barthelemy, Perrimond-Trouchet and Laborit)[7]. We have administered heparin under various experimental conditions:

1) Heparin as an adjuvant agent in recompression treatment.
2) Heparin and residual fixation of anatomical injuries.
3) Heparin as a prophylactic agent in decompression sickness.
4) Heparin as the specific treatment in decompression sickness.

In situation 1 vital prognosis for survival is better after heparin injection. The improvement occurs mainly in the pulmonary manifestations. Pulmonary symptoms are not amplified. In situation 2 no heparin effect is seen. In situation 3 decompression accidents are less severe and heparin produces a better recovery in animals. In situation 4 heparin is not satisfactory as the specific treatment of decompression sickness.

These experiments emphasize the efficacy of heparin when it is injected as an adjuvant agent or as a prophylactic agent in recompression treatment. In the first case, the prognosis for survival is improved. In the second case, the accidents appear at the same rate in control animals, but they are not so severe. We have noted the eupneic effect of heparin and have never had aggravation with heparin treatment.

In addition to the hypercoagulant effect of exposure to hyperbaric pressure, bubbles appear after pathogenic decompression in vessels and in tissue. The bubbles increase blood platelet clumping, agglutination of erythrocytes and formation of plasma flocculates which provoke thrombosis. Reflex vasoconstriction is produced. These phenomena provoke a circulatory disturbance which results in a stasis. The hypovascularization will be followed by an aggravation of pre-existing tissue injuries and also new injuries. These traumatic processes result in proteolysis and intra-tissue coagulation. Around the injured foci there will be an increased filtration of fibrinogen through more permeable vascular walls which will result in coagulation and isolation of the foci. All these phenomena result in an isolation of injured regions and in anoxia, which is the most important serious factor in decompression sickness.

On the basis of the above let us schematize the possible effect of heparin:

1) Heparin is a classic anticoagulant agent. It diminishes hypercoagulation which is due, first to vascular and tissue injuries and blood platelet agglutination (tissue and platelets thrombokinase), second to hyperbaric pressure exposures during treatment of bends.

2) Heparin is an antiproteolytic agent.

3) Heparin is a vasodilatory, anti-exudative and lipoprotein bundle scattering drug.

4) Heparin is an anti-adrenergic agent.

5) Heparin action results in hyperemia which combats anoxia by delaying definitive injury and decreasing the seriousness of the injury.

Neurologists and neurosurgeons regard heparin as a dangerous agent, but there is a great difference between anatomical and physiopathological brain softening, neurosurgical arteriocapillary injuries and the bends injuries due to mechanical (bubble) disturbances in young men free from vascular disease. In the latter the precipitating cause, the bubble, disappears under recompression treatment.

Treatment in men. Since animal experiments have shown that heparin never aggravates the signs of decompression sickness or adversely alters the prognosis in animals, and definitively improves them under certain conditions, it was then logical to experiment with this drug in human therapy. We have used heparin in five severe accidents, four cases of decompression sickness and one of air embolism. Doses of 50 to 100 milligrams twice a day were used. Our therapeutic results were promising. In the five cases we did not encounter aggravation of symptoms but, on the contrary, we had spectacular improvements when other treatments had failed.

Without saying that heparin is a miraculous drug, according to our personal experience this drug represents an important adjuvant agent in recompression therapy. In severe accidents we have the choice between (a) local anoxia and its consequences, i.e., bad vital or functional prognosis, and (b) the possibility of hemorrhage following heparin injection. We have chosen the second solution for the reason that hemorrhages are not frequent with the doses of heparin we employ. Its local action is theoretically beneficial. In animals, especially, there is no aggravation but, on the contrary, improvement. The use of heparin in man fully confirms this hypothesis. Nevertheless, heparin use, which is theoretically dangerous, should be limited to the following: decompression sickness or severe air embolism when functional or vital prognosis is bad; situations in which recompression treatment with classic adjuvants such as oxygen, gas mixtures with high partial pressures of oxygen, helium-oxygen mixtures, and drugs does not bring improvement; conditions in which dyspneic or coronary disturbances are prevalent; and prolonged loss of consciousness or coma occurring in spite of classic treatment.

INVESTIGATION ON THE VARIATIONS IN BLOOD HEMATOCRIT, BLOOD PROTEIN, AND PLASMA AND ERYTHROCYTIC SODIUM AND POTASSIUM

Among the hematologic modifications in addition to coagulation occurring under hyperbaric pressure, we have investigated in man the variations in hematocrit, blood proteins, total sodium and potassium, plasma sodium and potassium, erythrocytic sodium and potassium, and plasma and erythrocytic cholinesterases. Samples have been taken before exposure to hyperbaric pressure (situation 1), during stays at hyperbaric pressure (situation 2), and 30 minutes after returning to atmospheric pressure (situation 3) during two different simulated dive schedules, 60 meters for 12 minutes and 30 meters for 30 minutes. The same staff, same equipment, same sampling techniques as in the thromboelastographic study were used.

The durations of exposure at 30 meters and 60 meters were chosen in order to have a similar degree of supersaturation in the 120 minute tissue after return to the surface (coefficient 1.5), decompression rate being 20 meters per minute. Blood levels were done by a specialized laboratory at Marseille, except cholinesterase levels which were done at the Physiological Laboratory of the Science University of Marseille.

TABLE IIIA

	Hematocrit (%)		Protein (grams)		Cholinesterases (Meg/L) Plasma		Cholinesterases (Meg/L) Corpuscular	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
	12 minutes at 60 meters							
Before	53.4	4.5	76	6.6	87	11	110.6	3.8
During	52.1	4.6	76	5.5	88	12	111	5.3
After	52.1	4.6	76	5.8	91	11	111.1	4.1
	30 minutes at 30 meters							
Before	54	1.14	80	6	108	11	92	3.6
During	52	1.22	77	5	111	14	89	3
After	53	1.14	79	4.5	112	15	89	2.5

TABLE IIIB

	Potassium (Meg/L)						Sodium (Meg/L)					
	Total		Plasma		Corpuscular		Total		Plasma		Corpuscular	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
					12 minutes at 60 meters							
Before	58	10	5.3	0.19	107	19	94	8	147	5	46	15
During	53	8	5.2	0.18	97	14	96	9	142	6	51	10
After	53	7	5.1	0.19	96	9	94	11	141	7	50	10
					30 minutes at 30 meters							
Before	54	7.5	4.8		107	17	91	6	146	3.7	43	10
During	50	6.4	4.9		90	6.8	89	4.7	144	2.6	46	9
After	48	6.6	4.7		85	7.8	86	4.7	144	3.9	35	12

The following results can be seen in Tables IIIA and IIIB. Comparisons of hematocrit data obtained before, during and after exposure to hyperbaric pressure do not show important hematocrit variations. There were no blood protein variations at 60 meters and small differences at 30 meters.

At 60 meters the potassium concentration in both the whole blood and in the erythrocytes decreased between situations 1 and 2, and did not change from situation 2 and 3. There were no important changes in the potassium levels of the plasma. At 30 meters total and erythrocytic levels of potassium measured during the stay under hyperbaric pressure were significantly lower than those measured before the dive. They continued to drop after decompression. No variation was shown in plasma potassium.

At 60 meters very little variation was seen in total blood sodium concentration. Erythrocytic sodium increased during exposure to hyperbaric pressure and decreased during decompression. Its level remained higher that at the start (46 - 51 - 50). Plasma sodium decreased significantly during the stay under hyperbaric pressure. No new variation was recorded after decompression. At 30 meters the total blood sodium concentration decreases evenly in the transition through compression and decompression. Erythrocytic sodium concentration increased from 43 to 46 during stay under hyperbaric pressure, then dropped to 35 on return to atmospheric pressure. No important variations were seen in serum sodium concentration.

The erythrocytic cholinesterases did not show notable variations at 60 meters. At 30 meters, variations are very small. Serum cholinesterases show no significant rate variations at either 60 or 30 meters. Cholinesterases were measured[9] as microequivalents of acid freed in ten minutes.

It appears from this study that there are variations of K and Na levels in a 12 minute dive at 60 meters, as well as in a 30 minute dive at 30 meters. The major variations are:

1) a decrease in total potassium;
2) a decrease of erythrocytic potassium;
3) an increase in sodium concentration of erythrocytes;
4) a significant decrease in plasma sodium concentration during a simulated 60 meter dive.

Important differences are seen in the ionic levels of blood when comparing the data obtained before and during a stay under hyperbaric pressure. Variations are small after decompression. The observed alterations seem due to the stay under hyperbaric pressure. It is logical, therefore, to think that these variations, due to a stress, are increased by too rapid decompression.

Further experimentation will be necessary to delineate biological changes and determine their etiology. This work is in progress at GERS on animals. We have also started metabolic orientation studies concerning the phenomena due to hyperbaric pressure. Rabbits with acidosis show a decrease in ketone bodies in urine during a stay under a pressure of 10 atmospheres, using air as the breathing

mixture. This decrease seems to be due perhaps to a metabolic orientation toward the pentose cycle, which reduces the efficiency of the Emden-Meyerhoff and Krebs cycles.

We are also studying the alkali reserves, blood pH, and are carrying out electroencephalographic recordings and recordings from the brain by deep electrode methods. These investigations are done under various conditions including compression, exposure to sustained hyperbaric pressures with various breathing mixtures, and decompression.

In this manner we expect to delineate some physiopathological aspects of life under hyperbaric pressures, the understanding of which is necessary before starting serious experiments on man.

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COMMENTS ON THERAPEUTIC RECOMPRESSION

D. E. Mackay
Surgeon Lieutenant Commander Royal Navy
Royal Naval Physiological Laboratory
Alverstoke, Hants, England

During the past ten years the incidence of decompression sickness has increased in the Royal Navy. In the past such cases were usually the result of accident or negligence but now more cases arise from the testing of theories of decompression, training in buoyant ascent as a method of escape from submarines and the use of high altitude tests in the selection of aviators. I have collected records of past cases from this laboratory, from reports to Naval Medical Officers of Health, reports of Boards of Inquiry, hospital case notes, and reports of various diving trials. The majority of these cases occurred on board HMS RECLAIM. Due to the many people involved, these reports were rarely as comprehensive, consistent or detailed as would have been desired but they formed the source for a survey carried out last year by my colleague, Surgeon Lieutenant Commander Slark of the Royal New Zealand Navy, into the effectiveness of the therapeutic tables, as modified for use in the Royal Navy[1]. Since that survey I have been further involved in the treatment of 25 cases of divers' decompression sickness. As I have been associated with the treatment of decompression sickness in three aviators and, for the past five years, I have also acted as advisor in the treatment of decompression accidents at the Submarine Escape Training Tank, I hope that some of my opinions and prejudices might be of interest to others in this field.

DECOMPRESSION SICKNESS IN DIVERS

For the purpose of this paper, the term decompression sickness is limited to cases of sufficient severity that recompression is needed for the alleviation of signs and symptoms in the patients. Accordingly skin rashes, itches and other minor symptoms will not be mentioned further but this is not to be understood as meaning that these conditions are not real and troublesome.

Broadly speaking, two methods of therapy have been used, the slow continuous decompression method and the stage method, and the background is adequately described in the various papers published between 1939 and 1947 by Behnke with other workers, among them Yarborough, Duffner and Van Der Aue[2,3,4]. Based on this evidence, the Royal Navy changed from the Haldanian concept of a slow pressure release in 1952 and adapted the tables which first appeared in 1945 as Research Project X-443, Report No. 1 to British Diving Practice. This change in practice had been encouraged by dissatisfaction with the failure rate of therapy under previous routines, a figure of 50 per cent is quoted in the 1945 report and the 1947 analysis by Van Der Aue, Duffner and Behnke[3] suggested that the new routine could reduce this to about five per cent. In Britain, the figure is about 20 per cent. The evidence for this statement comes from the analysis by Slark with the addition of the cases occurring in the past year, as described in the following notes.

TABLE I

Patients	Number	Per Cent
Patients with pain symptoms only	101	62.4
Patients with other symptoms only	7	4.3
Patients with mixed symptoms	53	33.3
Total	161	100

Table I divides the 161 reports into three categories: patients with pain symptoms only, with symptoms other than pain, and with mixed symptoms. It agrees broadly with previous findings as to the proportion of cases where pain is present and where only other symptoms are present. It may still be true that other symptoms or signs were not disclosed when severe pain has made the diagnosis simple and treatment imperative. This in particular may apply to cases showing very early shock.

TABLE II

Symptoms	Number	Per Cent
Disorder of power	23	14.2
Disorder of sensation	15	19.3
Shock	12	7.4
Nausea and sickness	9	5.6
Vertigo	6	3.7
Headache	5	3.1
Unconsciousness	4	2.5
Disorder of vision	4	2.5

Table II describes the proportion of more serious symptoms that occurred and illustrates the point that most cases had two such complaints during one attack.

TABLE III

Symptoms	Number	Per Cent
Pain in upper limbs	83	51.2
Pain in lower limbs	34	34.0
Pain in torso	26	16.1
Pain in combinations of above	26	16.1

Table III is concerned solely with the incidence and distribution of pain. On the whole the evidence confirms the pattern found by Van Der Aue, Duffner and Behnke[3] but is in intriguing contrast with the findings of Griffiths et al[5] in the Dartford Tunnel where the relative incidences of arm and leg bends are reversed. One is tempted to assume that the supportive effect of water is a cause of the lower "leg bend" rate in divers.

TABLE IV

Treatment Table	Number	Recurrences	Rate Per Cent
Table 1	72	16	22.2
Table II	46	9	19.6
Tables III and IV	12	4	(33.3)
155/43	26	5	19.2
Other	5	3	(60.0)
Over-all	161	37	23.0

Table IV presents the method which was used to treat the cases with the number of times when subsequent recompression had to be used. 155/43 refers to the last edition of the Royal Naval Diving Manual in which the Haldanian slow pressure release method was used. Unfortunately there is some doubt in all the treatments as to the amount of oxygen used or even as to the actual routine employed; by this I mean that the term "American Table 2" on a report is more likely to mean the "British Modification of the Therapeutic Table 2A of the USN" than its apparent intention. I have therefore made no further subdivision of each

method but these are the major points of difference. In the Royal Navy, rapid surfacing from 30 feet has never been regarded with favor; equally, breathing oxygen at depths greater than 30 feet during a therapeutic procedure has not been encouraged. In fact, 100 per cent oxygen has very rarely been used at any stage. On Table II, the stop at ten feet has been taken as two hours instead of the recommended four, as it was felt illogical to have four hours on Table II at that depth, but only two hours on Table III and Table IV; and finally the time of ascent between stops is taken as five minutes instead of one minute. The section headed "other" contains (a) one case treated, with no success, on a continuous decompression method as recommended by Eaton[6] on the basis of his experience with goats; (b) two cases who were involved in an accident and were given an intermediate "preventive" recompression before their true condition was diagnosed; and (c) two cases following oxygen-helium diving which did not respond rapidly to compression to the equivalent of 165 feet but who cleared on being taken to 250 feet and who were then gradually decompressed to join Table II at 140 feet. I think it is legitimate to ignore the small number under "other" and under "Tables III and IV." The interesting fact is the relative constancy of the recurrence rate of the continuous decompression method and the two "stage routines."

TABLE V

Type of Case Treated	Number	Recurrences	Rate Per Cent
Pain only (Table I or II)	75	13	17.3
Other than pain (Table I or II)	41	13	31.7
Complicated but apparently properly treated	12	4	(33.3)

However Table V casts an interesting light on this "constancy" and demonstrates fairly clearly that the original assessment of the case is most important (the figures do not always cross-check because of the quality of the records). The obvious conclusion is that if cases are erroneously thought to be suffering only from the pain of a non-damaging form of bends, or from symptoms considered to be secondary to pain, then the failure rate will be almost double that arising after the treatment of a straightforward case if the same table is used. The disheartening thing is the number of cases in which a recurrence arises after the long therapy involved in Table III or Table IV, even if this number is too small for a firm conclusion as to its efficiency. After all, a recurrence may well be considered an excellent result where death is the alternative. The effect of the speed with which treatment is given may be deduced from the information in Table VI.

TABLE VI

Time of Onset	Number	Recurrences	Rate Per Cent
On or before surfacing	55	10	18.2
Within 1/2 hour	27	10	37.0
1/2-4 hours	33	5	15.2
Over 4 hours	16	1	(6.3)

Regrettably where the time to onset of symptoms was given in a report, only very rarely was it possible to find the interval before treatment was given. From my own case, and I think it is reasonable to assume other people would have a similar routine, if therapeutic recompression is ordered, then it is usually begun quickly. Certainly it is begun within one-half hour in the majority of cases. Since delay tends to produce more serious symptoms and leads to a more recalcitrant bend, the delay in treating limb bends is as short as possible and in more serious cases almost non-existent. The delay was as short as 18 seconds from developing trouble in one case. An intriguing and so far inexplicable figure to me is the recurrence rate for those cases developing between surfacing and one-half hour later.

RELEVANCE OF OTHER TYPES OF DECOMPRESSION SICKNESS

The main groups of people who might contribute to a greater understanding of this problem are tunnel workers, aviators and submariners. One must assume that in a diver, decompression sickness arises in a tissue supersaturated with the appropriate inert gas and symptoms are a consequence of bubble formation. In tunnel workers a similar supersaturation occurs on return to ground level, but commercial and other applications of high air pressures had led to use of different therapeutic regimes. Under present instructions the diver, except in relatively minor cases, is recompressed to 65 psi, equivalent to 165 feet and the subsequent decompression will take approximately 10, 20, or 40 hours. This therapy is almost entirely independent of his original exposure to pressure. Griffiths[5] at Dartford Tunnel started off by returning his cases to a pressure 2 to 3 psi above the original working pressure and on rare occasions as much as 10 psi above, but he had a one-third recurrence rate. In spite of following recommended decompression routines the best he could achieve was a 10 per cent recurrence when he nearly doubled the decompression time by slowing down the rate of steady decompression from 9 min/psi to 15 min/psi. However, when he changed to a routine determined by using the depth of relief of symptoms his minimum effective initial treatment pressure, followed by standard working decompression procedure, his recurrences dropped to 1 man in the 50 cases of bends with pain alone. For the more serious cases he eventually devised a routine which involved 15 to 20 hours therapy with "soaks" at 8 psi, 4 psi and 2 psi levels. With this there were no recurrences in 16 cases.

Following several suggestions by eminent Americans in the past 25 years, aviators have at last treated apparently moribund cases of decompression sickness collapse syndrome by compression to greater pressures than one atmosphere. The first report in the United States dealt with a patient who was treated under naval diving auspices with the appropriate long therapeutic table. In some ways one may regard the aviator as a dweller of the heights who did not have adequate decompression after his dive to an ambient pressure of 15 psi. Accordingly, those serious cases where symptoms were not relieved by return to "working pressure," i.e., ground level, should be further recompressed. The first case was regarded as a diver and was so treated because of his serious symptoms on the long table. Colleagues of mine using a high altitude test for the selection of aviators decided to use other methods on any candidates whose bends did not clear quickly; one case has already been reported and a paper by Cannon and Gould[7] on six such cases is now in press. Against my advice, though after considerable discussion and debate, their policy is to use the symptoms and signs of the patient as a guide to the eventual "over pressure" required and to the rate of decompression. Symptoms have recurred in at least two cases during decompression but a return to a pressure of 5 psi greater than the level of recurrence has been adequate to clear trouble and permit the continuation of decompression. There is no doubt that in one case it has saved a life. Certainly not one of the doctors at the Royal Naval Air Medical School would subscribe to the suggestion that supportive therapy alone is the best treatment for aviator's decompression sickness present at ground level, with recompression only as a last resort. This attitude appears to be endorsed by our RAF colleagues who have been receiving instruction in the management of chambers and patients.

So far I have described the situations and treatments of cases where bubbles arose in a supposedly supersaturated tissue. In submarine escape training by buoyant ascent, the bubbles may be introduced via the blood stream into the circulation of an unsaturated tissue by some accident. The abrupt mechanism of bubble introduction means that such cases usually are presented for treatment with serious symptoms. Collapse and unconsciousness are not rare. Recompression is the most important part of treatment and speed is essential for a successful result. At HMS DOLPHIN we have found that it is almost pointless to stop at a pressure less than 165 feet even when pain has been the presenting symptom and the patient is apparently completely well on recompression to 60 feet. However, in many cases, for the purposes of subsequent decompression, we have regarded the patient as having had a dive to 165 feet for a total period of his previous pressure exposures that day, plus 30 minutes that he should remain at 165 feet. Broadly if a patient was trouble-free on arrival at 165 feet he was treated as a diver and returned to the surface in about two and one-half hours. However if any sign or symptom persisted on arrival at that depth he was treated on Table III or IV as appropriate. The recurrence rate is much smaller so far than with the manual routines and usually such a case arises when the idea is stretched to cover those who arrive at 165 feet with some symptom which may clear fairly rapidly during the 30 minute wait, but again numbers are still too small for definite conclusions, even if the idea is promising.

DISCUSSION

As well as considering the mechanism leading to decompression sickness, one must consider other matters. An important factor is the instruction given to the person responsible for treatment. A recurrence rate of 50 per cent belies the air of confidence in the dogmatic orders accompanying the tables which suggest, "follow this routine and all will be well." The discomfort of decompression sickness, the confinement in a small metal cylinder, the noise of frequent air changes to prevent carbon dioxide accumulation (and also prevent restful sleep), the loss of taste of food, the lack of comfort in toilet arrangements or bedding, and the resistance to breathing from increased density of air or from auxiliary breathing equipment, make the whole process very exhausting and may cause consequent complications for the patient. This might be justified if one could promise success, but the prospect of spending up to 40 hours more after an initial six to ten hours can be most demoralizing for patient and attendants. My heartfelt sympathies are extended to a London team who spent nine days with a patient in a chamber.

These points logically lead to the suggestion that the treatment of decompression sickness needs revision. There has been a period of nearly 20 years in which the present routines have shown a considerable advantage over the previous methods. The authors of existing methods are certainly deserving of honor but I am sure they would not be surprised that time has led to a new viewpoint especially as the tables were developed to <u>prevent</u> decompression sickness rather than to <u>treat</u> it when it disclosed itself. It may well be that the tables as modified by the Royal Navy and as operated by personnel trained in the British manner are not as satisfactory as when they are used on their home ground in the United States. It may be that the diagnosis of decompression sickness has to be clarified so that proper decisions can be made. It may well be that an extra routine should be developed using the depth of relief as a guide, rather than automatic exposure to higher partial pressures of nitrogen than might be needed.

CONCLUSIONS

I have no intention of abandoning routines of the diving manuals, though I reserve the right to deviate when I consider this is in the best interests of my patient. As my opinion is fallible, I may make mistakes and therefore I have a cautionary tale for those who may want change for change's sake. Recently, during some oxygen-helium experiments in dives to 300 feet, errors occurred in the decompression drill and a pair of divers developed chokes at ten feet. They were immediately recompressed and were symptom free at 30 feet. Examination at 100 feet was completely negative so, under constant observation, decompression on Table I (British modification) was commenced. It was assumed that the speed of recompression would be beneficial. The treatment was successful. Later, a similar case arose and the progress was similar till after 25 minutes at 100 feet, before the first movement in therepeutic decompression, the patient developed cold feet and numbness in his thighs. Immediately he was further recompressed to 165 feet, with relief of symptoms, and Table IV was ordered with a two hour wait at 165 feet. However, during those two hours he developed complete motor and sensory loss from the level of the tenth dorsal vertebra. "Depth of relief" is ambiguous in his case. "Return to working

pressure" posed a problem in subsequent decompression. Symptoms definitely persisted after two hours at 165 feet but the case was undoubtedly decompression sickness.

I now see this diver fighting his way back to health and I do not know whether I was responsible for his condition or whether he was going to have serious trouble whatever therapeutic regime might have been used.

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EXPERIENCE WITH MODERATE HYPOTHERMIA IN THE TREATMENT OF NERVOUS SYSTEM SYMPTOMS OF DECOMPRESSION SICKNESS

A. Erde
Lieutenant, Medical Corps, U.S. Navy
U.S. Naval Submarine Base
Pearl Harbor, Hawaii

THE PROBLEM

About ten per cent of the cases of decompression sickness, the so-called "serious cases," exhibit involvement of the central nervous system. While the spinal cord is most commonly involved, presumably because of the large amount of nitrogen gas dissolved in its high lipid and myelin content[1], the brain is also affected in many cases. Commonly, these serious cases follow extreme exposure to depth, usually involving very deep dives or multiple dives for extended periods of time, with inadequate or no decompression and with considerable delay in obtaining recompression treatment. Standard treatment of the underlying decompression sickness by recompression and subsequent controlled decompression in a decompression chamber almost uniformly relieves the pain and other symptoms of minor cases of the bends in a rapid and dramatic fashion. However, it often fails to prevent or alleviate central nervous system symptoms which follow severe decompression sickness.

The physical presence of bubbles of nitrogen gas primarily which are formed intravascularly and extravascularly has been postulated as the cause of the symptoms of decompression sickness[2,3,4]. Whether these bubbles are carried to the nervous system as microscopic or macroscopic air emboli via the vascular system, or form from the appreciable amounts of nitrogen dissolved in the lipid-rich nervous tissue subjected to high partial pressures of nitrogen gas in diving and caisson work, the insult to the tissues that they produce is held responsible for the subsequent development of edema of the affected nervous tissue, with the production of coma, convulsions, and motor and sensory deficits affecting the cranial and peripheral nervous systems[1].

Moderate whole body hypothermia has been employed in several severe bends cases in which evidence of central nervous system edema was noted as a complication. It was used in an effort to reduce the formation of the edema itself and to counter its adverse effects upon the nervous tissue. The following analysis of seven cases of decompression sickness affecting the central nervous system (see Addendum for case histories) illustrates the results of recompression-decompression treatment with and without hypothermia. The cases selected were those exhibiting severe nervous system symptoms treated immediately prior to and following the use of hypothermia at the Pearl Harbor base. They present rather typical symptoms of decompression sickness effects upon the nervous system, and indicate the effect of adding hypothermia to the treatment program. All of these patients were civilian amateur or semi-professional SCUBA divers who were stricken while diving in Hawaiian waters.

CLINICAL DATA

Divers designated I, II, III and IV in this section refer to patients treated without hypothermia; those designated V, VI and VII were treated with hypothermia. These designations correspond to those used in the Addendum.

REPETITIVE DIVES. All of the divers studied in this survey made repetitive dives with substantially no decompression. All of the repetitive dives exceeded the limits of the U. S. Navy repetitive diving tables for no-decompression diving, and are summarized in Table I.

TABLE I

Outline of Dives Made

Diver	Number of Dives	Depth/Time of Dives ( ) = no. of dives
I	3	110/25 (3)
II	3	125/25 (2), 40/30
III	4	90/5, 120/30 (2), 30/30
IV	5	100/25 (5)
V	4	130/20 (4)
VI	3	160/20 (3)
VII	5	165/15 (3), 165/5 (2), 120/20 (2)

Close questioning of each diver revealed that his estimates of depth and bottom time were approximations, and usually on the conservative side. No diver used a depth gauge, lead line, or wrist watch. All were more than a little sheepish about having contracted the bends, and tended to minimize these data.

TIME ELAPSED BETWEEN ONSET OF SYMPTOMS AND TREATMENT. Data presented in Table II is based upon estimates made by the divers in their medical histories or by their companions. In general there was no marked disparity between the two treatment groups as regards delay in receiving recompression treatment.

LEVEL OF SPINAL CORD LESIONS. With the exception of Diver V, who had brain and cranial nerve symptoms, these divers exhibited spinal cord lesions of varying degree. The level of the cord lesions is outlined in Table III.

TABLE II

Elapsed Time Between Onset of Symptoms and Recompression Treatment

Diver	Elapsed Time (min)
I	240
II	300
III	180
IV	270
V	180
VI	300
VII	180

TABLE III

Level of Spinal Cord Lesion

Diver	Cord Level
I	L-1 to L-2
II	L-2 (some sacral sparing)
III	T-9 to T-10 (some sparing of L-3 to L-4)
IV	T-8 to T-9
VI	T-10
VII	L-1 (hemi-cord lesion)

EVALUATION OF SEVERITY OF SYMPTOMS. A strict comparison of the extent and severity of nervous system involvement in these patients cannot be made because of the diversity of the exposures to pressure and of the different locations and extent of the lesions. However, it is noteworthy that, with the exception of Diver V, all men suffered marked paresis or paralysis of muscle groups

in one or both lower extremities as well as sensory abnormalities. Bladder and bowel function was impaired in all but Divers II and V. Superficial reflexes were altered in four of these men; two who did not receive hypothermia (III and IV), and two who did (VI and VII). No mention was made of changes in these reflexes in Divers I and II, and they remained normal in Diver V. The deep tendon reflexes of the lower extremities were abnormal in the first four divers, hyperactive in Divers I and III, depressed in Divers II and IV. They were depressed in the extremities of Divers VI and VII as well (and unaffected in Diver V). Bowel and bladder function were adversely affected in all but Divers II and V. In general it can be said of all except Diver V that these patients sustained severe lesions of the spinal cord. Diver I was the only patient who suffered from marked shock, requiring support of his blood pressure. Diver V was the only man who suffered from brain and cranial nerve effects of his decompression sickness.

EVALUATION OF RESIDUAL DEFECTS. The crux of the assessment of the efficacy of hypothermia and the other treatments furnished these stricken divers is the extent to which their deficits were restored. Length of follow-up evaluations varied widely for these divers. However, the following generalizations (excepting for Diver V) can be made, on the basis of the patients' condition from seven to ten days after receiving decompression, with or without hypothermia.

All divers had residual motor weakness in one or both lower extremities. Divers VI and VII had relatively little motor residual weakness, Diver I had a moderate residual defect, Divers II and IV had serious defects and Diver III had complete paraplegia. All except II and V had persistent sensory defects. The sensory deficits remaining in Divers I, VI and VII were minimal compared to their initial losses, and when compared with the less complete recoveries of Divers III and IV. Bladder function was impaired in Divers I, III, IV and VI, and restored to near normal in VII. Bowel function was impaired in Divers I and III, improved in IV, and nearly normal in VI and VII. No neurologic deficit persisted after the decompression treatment of Diver V. Table IV summarizes residual defects in these divers seven to ten days after decompression treatment.

DISCUSSION

PATHOLOGIC FINDINGS IN THE CENTRAL NERVOUS SYSTEM. Death following severe central nervous system involvement in cases of decompression sickness was more common in the late nineteenth and early twentieth century than in recent years[2]. Pathologic findings in autopsies performed immediately after earlier diving or caisson accidents included the presence of free gas in the vessels as well as within the nervous tissue. Microscopic and macroscopic hemorrhages and areas of gross edema were described in the cord and brain[3,4]. Ischemic necrosis, tearing, and separation of tissue and fibers by gas formation were also noted. Congestion of the brain and spinal cord with microscopic areas of softening were observed, especially in the lower dorsal cord. The white matter of the cord was found to be more frequently affected by necrosis than the grey, the posterior columns and posterior portions of the lateral columns especially[1,2].

Patients succumbed weeks to months after the initial attack, usually to bladder and bed sore infections or pneumonia, softening and disorganization of the

TABLE IV

Residual Defects

Diver	Motor	Sensory	Reflexes	Bladder	Anal Sphincter
I	*	*	0	*	**
II	**	0	*	0	0
III	***	**	*	*	**
IV	**	**	**	*	*
V	0	0	0	0	0
VI	*	*	0	*	*
VII	*	*	0	0	0

0 denotes little or no residual deficit. *indicates severity and extent of residual deficit.

brain and cord substance, edema, hemorrhage, sclerotic cavities, and gliosis of the nerve tracts of the cord, basal ganglia, corpus striatum, and other areas[2,3].

BUBBLES AND CENTRAL NERVOUS SYSTEM EDEMA. Gas bubbles have been postulated and demonstrated in both the intravascular and extravascular spaces of the nervous system in decompression sickness[4,5,6]. The insults to the nervous tissue produced by these bubbles are held responsible for the pathologic changes and neurologic effects ascribed to decompression sickness. Suggested relationships between these factors are indicated in Figure 1. Intravascular gas bubble emboli, both microscopic and macroscopic, block circulation to nervous tissue, producing vasospasm, tissue anoxia, and ischemic necrosis[7,8]. The vasospasm produced may lead to cerebral or spinal cord edema[9], and contribute to the anoxia, ischemia, and necrosis of the tissues, which, in turn, produce additional vasospasm. Gas formation within the substance of the nervous tissue produces separation and tearing of the tissue as well as hemorrhage. This trauma contributes further to the damaged tissue state.

The distinction between extracellular swelling and intracellular cerebral and cord edema is probably of academic interest only in this disease, since both forms of edema have been described in cases of decompression sickness and induced in animal experiments dealing with the effects of anoxia and micro-emboli upon the central nervous system[7,8]. Intracellular edema has been ascribed to huge swelling, vacuolization, and multiplication of the epithelial cells of the choroid plexus, ependyma, and oligodendroglia after such trauma has produced nervous tissue damage[10]. Prompt increase in the secretory activity of the choroid plexus, ependyma cells, and oligodendroglia produces increased free

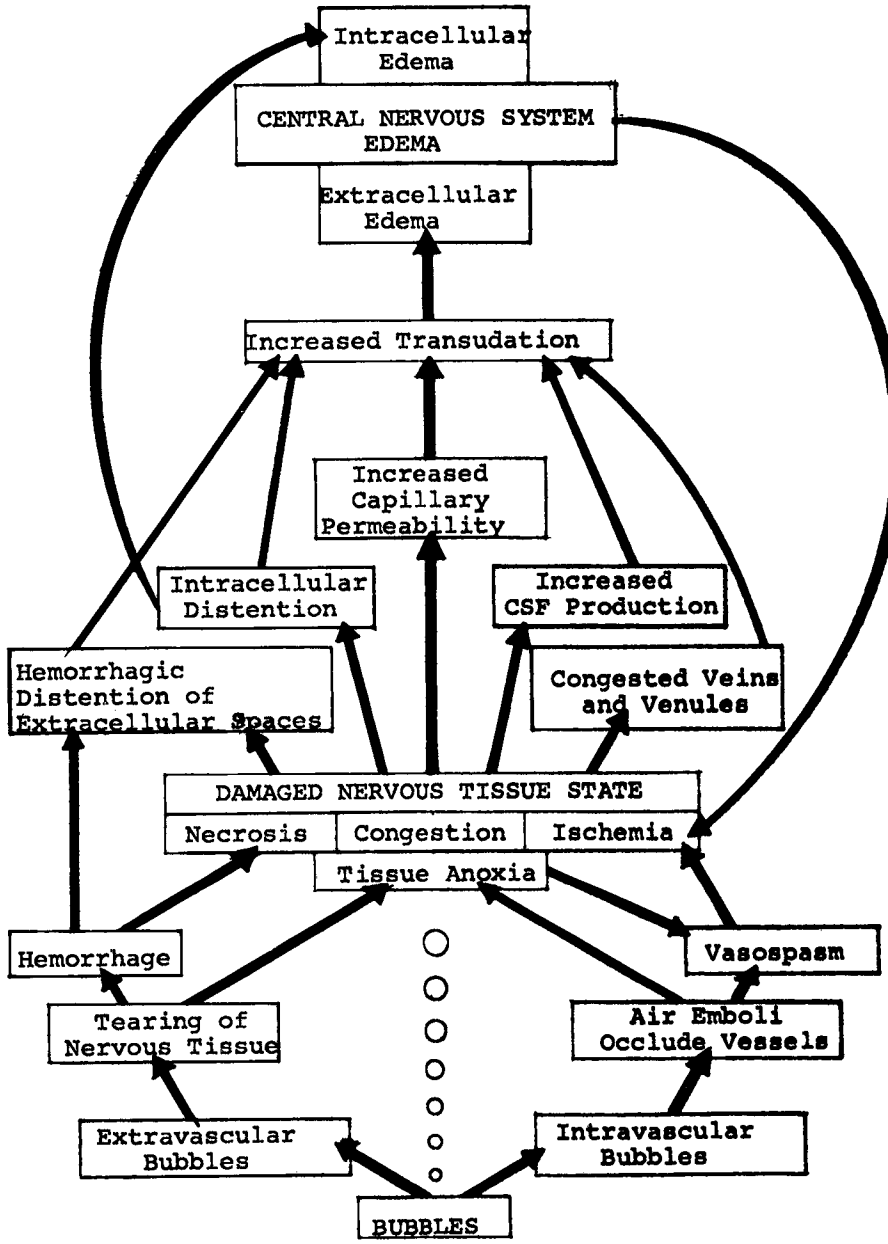

Figure 1. Suggested relationships between intravascular and extravascular bubbles, nervous tissue damage, and nervous system edema.

fluid in the ventricular system and a distention of the extracellular spaces between epithelial cells, the perivascular areas, and between fascicles of myelinated nerve fibers of the white matter with transudate fluid. Nervous tissue anoxia contributed to increased capillary permeability and filtration of fluid and protein into the perivascular extracellular areas[11]. Resultant extracellular edema is also enhanced by transudation from congested cortical and spinal veins and venules. Hemorrhage, when present, contributes to tissue anoxia and ischemia, increasing the transudation of fluid into the extracellular spaces. This vicious cycle is sustained by the feedback effect of the nervous system edema in increasing congestion, ischemia, and necrosis of the affected nervous system areas, thus favoring the formation of additional edema[12]. Persistence of edema alone, after controlled decompression and artificial breathing mixtures have resolved the bubbles which produced the initial insult, is sufficient to induce partial or complete interruption of function of affected portions of the nervous system without additional pathological mechanisms.

CENTRAL NERVOUS SYSTEM EDEMA AND HYPOTHERMIA. Moderate hypothermia was selected for treatment of nervous system edema because of several striking advantages that it affords. It has a direct effect upon the progression of edema itself, believed due by some to the lowered cerebrospinal fluid and blood pressures produced. Its physical and metabolic effects tend to counter the pernicious effects of edema and gas trauma upon nervous tissue function. In whole body hypothermia, metabolic and oxygen requirements of nervous tissue are markedly reduced, thus protecting the tissue from the effects of relative hypoxia[13]. In addition, cord and brain volume are reduced, and increased intracranial space is provided in many cases[14]. This modality would appear to help break the cycle demonstrated in Figure 1, help prevent further tissue damage, and favor functional recovery of anatomically intact nervous tissue after the bulk of excess inert gas has been safely removed.

SUMMARY AND CONCLUSIONS

Experience with moderate hypothermia at the Pearl Harbor Submarine Base has been limited; only a few serious cases have been treated. However, evaluation of the course of serious cases reveals that seemingly adequate decompression schedules with artificial breathing mixtures do not relieve or prevent many or all symptoms of nervous system trauma. While part of the symptomatic picture may be ascribed to persistent gas foci within the nervous tissue, a great deal of the clinical picture conforms to the development and persistence of edema in these tissues despite protracted and even multiple courses of decompression. Patients treated with moderate whole-body hypothermia in addition to standard decompression appear to experience relatively prompt relief of such symptoms, in some cases before decompression has been completed. The subsequent rapid regression of motor and sensory losses has impressed physicians experienced in treating diving casualties as well as the neurologists caring for these divers during subsequent hospitalization. On the basis of very limited clinical experience as well as on theoretical physiological grounds, hypothermia appears to be a practical and efficacious treatment for edema of the central nervous system when it develops in serious cases of decompression sickness.

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ADDENDUM

Case I (JS)

This forty-three year old Hawaiian-Chinese diver, with nine years of SCUBA experience, made three dives deeper than 110 feet for not less than 25 minutes. His surface intervals were less than 15 minutes, and he took no decompression. Shortly after surfacing from the third dive, he noted the rapid onset of severe pain in the low back and abdomen. He decided to treat himself for the bends by decompressing on the anchor line of his boat. However, a strong current prevented his leaving the descending ladder (depth 3-5 feet) to which he clung for about 30 minutes, at which time exhaustion and pain forced him back into his boat. Nausea developed, and the acute lumbosacral and abdominal pain doubled the diver up.

Four hours after his last dive this man arrived at the Submarine Base, Pearl Harbor, complaining bitterly about the severity of his pain. Physical and neurologic findings were within normal limits. Motor and sensory function of the lower extremities was normal. Recompression was initiated, and at 60 feet pain was almost completely relieved, and the patient was able to stand and walk easily. He was taken to a simulated depth of 100 feet, and decompression treatment started. After nine minutes at the 60 foot stop, 53 minutes after reaching the bottom, back pain returned, and dizziness and numbness in both feet were noted. The patient was unable to stand unaided. The chamber was taken to 165 feet of simulated depth, and a longer table of treatment was started. Over the following 30 minutes the symptoms of his neurologic injury unfolded. He lost perception to pinprick in the entire lower right extremity, and from midthigh distally in the lower right extremity. The left lower extremity displayed weakness in all hip, knee, and ankle motion. Dorsiflexion of the left ankle was entirely absent. The patient was unable to void voluntarily.

About five and one-half hours after the start of treatment the patient's blood pressure became unobtainable, and his limbs grew cold. An intravenous drip of levarterenol bitartrate was required to sustain his pressure for the next 12 hours. The patient's urine output (indwelling catheter) was less than 20 ml/hour for the first 18 hours of treatment. He was given six liters of intravenous fluids during the first day of treatment, and urine output rose to 300-400 ml/hour subsequently. The urine was found to contain many hyaline and granular casts. The patient was conscious and well-oriented throughout the treatment period, and was given 0.1 gram of phenobarbital every four to six hours intramuscularly for restlessness.

Little change in neurologic status was observed over the course of decompression treatment. At the end of the 38 hour treatment period, hyperactive ankle and knee jerks bilaterally and bilateral Babinski reflexes were present, signs of upper motor neuron abnormality. After one week of subsequent hospitalization, sensation in the lower extremities had returned to normal, except for the feet. The diver had normal motor power in the lower extremities except for almost complete loss of dorsiflextion of the left ankle. He had had a few voluntary bowel movements, but still required supplementary enemas. He had not established bladder control, and required an indwelling catheter.

Case II (RT)

This twenty-eight year old Hawaiian male, with nine years of diving experience and a prior pain-only shoulder hit, had noted pain in the right gluteal and right sacroiliac area shortly after surfacing from his first dive of the day to about 120 feet for 20-30 minutes. Weakness was then perceived in the right lower extremity, and the pain increased in severity.

The diver returned for another dive to the same depth, and the symptoms disappeared shortly after he reached the bottom. After surfacing from the second dive, the symptoms recurred immediately. After an hour surface interval, with no remission of the pain, the diver moved to forty foot water, and made his third dive to relieve the pain. After ten minutes, while still on the bottom, the pain and weakness returned. The diver stayed at about 40 feet for 30 minutes until the constantly increasing discomfort drove him to the surface.

Three hours after surfacing from the third dive, the diver was brought to the Pearl Harbor Submarine Base. Examination revealed a moderately obese, alert male sitting in a chair with all of the joints of his right lower extremity extended, and his right hand pressing his lower back. He was unable to walk, and was assisted into the chamber. Physical and neurologic findings were within normal limits except for marked muscle weakness and decreased sensation to light touch and pinprick in the entire right lower extremity. Deep tendon reflexes were brisk and equal, and no Babinski reflex was elicited.

At 165 feet of simulated depth, no immediate symptomatic improvement was noted. After remaining at that depth for several minutes, the diver noted slight relief of back pain, and was able for the first time to move his right lower extremity against moderate resistance.

Slow improvement was noted over the first seven hours of decompression. Then the right patellar and achilles reflexes became weak. At the 50 foot level, the patient noted marked decrease in pain and weakness, although the reflexes were still depressed. Motor power in the extensors and flexors of the right thigh was diminished. Bladder function was good.

The remainder of the decompression was accomplished without incident. Twelve hours after leaving the chamber, the reflexes were still absent, and weakness of all right gluteal and thigh muscles persisted, as did some pain. The patient was recompressed and decompressed again, using helium-oxygen breathing mixture and pure oxygen at the shallow stops. Very slight improvement in the residual symptoms was noted after the second decompression schedule. Ten days after completion of treatment, this diver was able to give up his crutches, but the strength in the affected thigh and gluteal muscles had not returned to the point where he could walk without a marked limp.

Case III (HH)

This eighteen year old white male, who had been SCUBA diving for two years, made a dive to about 90 feet with a partially charged bottle, and was forced to return to the surface rapidly. He donned a full bottle, and made his second dive of the day to more than 120 feet for 30 minutes. A third dive of same depth and duration was followed by the onset of right shoulder and bilateral hip pain. He treated himself by diving to 30 feet until arrangements were made to transport him from the Island of Maui to the Pearl Harbor base on the Island of Oahu by air.

Two hours after leaving the water the patient arrived at the treatment facility. Physical examination revealed a well-developed male in moderate distress from right shoulder and bilateral hip pain, and numbness from the waist down. He was able to walk with support, but evinced marked weakness of all muscles of both lower extremities. The patient was recompressed to 165 feet of simulated depth, and decompressed breathing a helium-oxygen mixture.

Shoulder pain was completely relieved at the end of the recompression. Deep tendon reflexes of the lower extremities were hyperactive, and there was clonus of both patellar and achilles tendons. Gradual diminution of all sensation was noted from the level of the

twelfth rib anteriorally to the umbilicus, becoming absent at the midthigh level on both extremities. Proprioception was absent from the lower extremities, where the patient was unable to move any muscle with the exception of a few faint flickers in the left thigh adductor group and the left gluteus maximus.

During the course of the decompression there was a shifting level of sensory loss. The patellar and achilles reflexes changed from initially hyperactive to weak, and then absent, as did the clonus. The patient settled to a picture of a cord transection at the level of T-9 to T-10, with some slight sparing of L-3 and L-4. To promote osmotic diuresis, he was given three units of intravenous urea in invert sugar solution. Attempts to institute moderate hypothermia were unsuccessful and abandoned when shivering could not be overcome; the lowest rectal temperature achieved was 95° F for a brief period. After eight hours at the 30 foot level with no improvement, the patient was returned to 165 feet for a second decompression table. This did not affect the paraplegia.

Three months after his release from the chamber, this patient could walk 135 steps unaided in a festinating manner. Superficial abdominal, anal and cremasteric reflexes were absent, achilles and patellar reflexes were hyperactive with sustained clonus, and bilateral Babinski reflexes were present. Motor weakness of dorsiflexion of both feet and knee, thigh, and gluteal muscles on the right remained. Sensory losses, lack of bowel and bladder control, and swelling and warmth of the lower extremities persisted. Six months after treatment, right foot drop, lack of bladder control at night, and infrequent normal bowel movements persisted. Hyperactivity and clonus of reflexes persisted, as did the bilateral Babinski reflexes. Motor weakness was limited to a reduced right foot drop; sensory loss persisted to a moderate amount in both lower extremities.

Case IV (FF)

This thirty-five year old white male made five dives to depths ranging between 30 and 100 feet in a three and one-half hour period which involved hard swimming against strong currents. Shortly after the final dive he noted pain in the epigastric and lower anterior chest area and numbness of the entire body below the nipples, with subsequent complete paralysis of the lower extremities. All of these symptoms cleared in the two and one-half hour interval between his last dive and his arrival at the Pearl Harbor Submarine Base. Physical examination revealed a healthy adult male in no distress. Neurologic examination revealed no abnormality except abdominal, anal sphincter, and cremasteric reflexes.

Over the following hour the diver complained first of a generalized tired sensation in both lower extremities with a "strained feeling" along a small area of the left lateral thigh. During the next hour he developed a perceptibly ataxic gait associated with weakness of both lower extremities, more marked on the right, affecting in particular the flexors of the right knee, the extensors of the right ankle and toes, as well as the extensors of the left knee. Numbness increased to involve the dorsal surfaces of both feet, with definite early hypalgesia. No sensory defect of touch, proprioception, or vibration perception was noted. The left patellar reflex was stronger than the right.

The patient was recompressed to 165 feet, and over the next three hours the level of subjective paraesthesias and increased motor weakness rose in both extremities, while deep tendon reflexes became progressively weaker. The level of hypalgesia reached the costal margins anteriorally, and the level of the third lumbar vertebra posteriorly. The patient was returned to 165 feet twice in the face of worsening cord symptoms, and placed on a helium-oxygen breathing mixture. Despite recompression his weakness increased over the following five hours, resulting in no antigravity motion in the right lower extremity, and very weak motor power in the right. The patient was incontinent of flatus and unable to

move the bowels. A reflex ileus produced moderate distention of the abdomen. Urination occurred in dribbles only.

Slight improvement in motor weakness was observed 15 hours after recompression. After leaving the chamber the patient walked with a markedly ataxic gait, and had moderate bilateral motor weakness of both lower extremities. One month after decompression his gait was slightly ataxic, bowel function was nearly normal, and urinary incontinence was intermittent. Paraesthesias persisted in the right calf, dorsum of the right foot, and in the parasacral and lower mid-back areas. Superficial reflexes were still absent. Deep tendon reflexes were more active in the right lower extremity, unsustained clonus was present in the right ankle and no Babinski reflex was elicited.

Case V* (ST)

This twenty-four year old Hawaiian-Japanese diver made four dives to over 130 feet for 20 minutes, swimming strongly. Ten minutes after surfacing from the fourth dive, he noted the sudden onset of sharp pain in both shoulders and elbows, and mild bilateral knee pain. Thereafter his vision became blurred, his speech thick, and the diver felt dizzy and unable to stand erect. Forced to lie at the bottom of the diving boat, the diver noted that he could move his extremities only with difficulty.

Three hours later, he was brought to the Pearl Harbor Submarine Base. Abnormal findings consisted of limitation of movement in all extremities by extreme joint pain. This pain was completely relieved as the chamber passed 110 to 120 feet of simulated depth. After forty minutes of recompression at 165 feet the diver experienced severe nausea, vomiting, and frontal head pain. Disconjugate eye motion was noted. The patient became hyperactive, thrashed about in the chamber, and was unresponsive to questions. After one hundred minutes of decompression, the patient remarked that the head pain was more severe, and he was unable to focus his eyes and complained of marked photophobia. His pupils were equal and only sluggishly responsive to light stimulation.

The chamber was returned to 165 feet, the patient given magnesium sulfate and meperidine hydrochloride parenterally. He was switched to a helium-oxygen breathing mixture, and cooled by surrounding his body with ice-filled plastic bags, while the chamber was vented very frequently. Intramuscular chlorpromazine was administer to prevent shivering. The patient's temperature reached and stabalized at 93.5° F (R) to 94° F (R) within forty minutes. Other vital signs remained stable and within normal limits during the remainder of the course of treatment. Gradual progressive improvement in the patient's status was noted after initiation of the above measures. Five hours after institution of hypothermia, the head pain, nausea, vomiting and photophobia had cleared completely. The only abnormal finding was a slight lag in the movement of the right eye. The ice was removed, and the patient's temperature reached 98° F(R) ninety minutes later. At no time during treatment did the patient's temperature rise above 99° F. During the remainder of decompression, the patient was asymptomatic and comfortable. Eleven months following treatment, no neurologic or other symptom had recurred.

Case VI (JM)

This thirty-five year old Hawaiian male had made three dives of about 20 minutes duration to over 160 feet in a three hour period. Shortly after the third dive, sudden

*This case was presented at the Second Far East Session, American College of Physicians, Tachikawa Air Force Base, Tachikawa, Japan on 12 May 1962.

numbness and weakness of the right lower extremity developed. This faded completely after an hour. Over the following three hours he noted the onset and progression of numbness and severe muscle weakness in the left leg, and the recurrence of symptoms in the right lower extremity.

Examination five hours after his third dive, at the Pearl Harbor Submarine Base, revealed partial atonic paralysis of the left lower extremity, with anti-gravity motion elicited only in the hip extensors, hip and thigh adductors, and ankle and foot extensors. Weakness was noted in all muscle groups of the right hip, leg, and foot, but to a lesser degree than on the left side. Slight weakness of the right hip extensors and adductors was noted. There was epicritic light touch to just below both knees, and loss of pain sensation to pinprick distally from just above the symphysis pubis anteriorly and the fifth lumbar vertebra posteriorally. Superficial abdominal and cremasteric reflexes were absent. Achilles and patellar reflexes were equal, but less brisk than those of the upper extremities. An equivocal Babinski reflex was present bilaterally.

No symptomatic change was noted during descent to 165 feet. The diver was given a helium-oxygen mixture to breathe. After one hour without symptomatic improvement, hypothermia was initiated by surrounding the patient's body with ice-filled plastic bags, and venting the chamber frequently. Shivering was prevented with periodic intermuscular injections of chlorpromazine. The patient's temperature at the start of cooling was 103.2° F (R). His temperature reached 94° F (R) within 30 minutes of cooling, and was kept between 92° F and 94.2° F during the course of hypothermia, except for one spike to 95° F and one dip to 90°. After two hours of cooling, no voluntary movement in either lower extremity could be elicited except for slight bilateral extension and adduction of the hips. The deep tendon reflexes of these extremities had disappeared, and marked weakness of abdominal muscles and relaxation of the rectal sphincter developed. The chamber was returned to 165 feet, and two hours later the patient was able to perceive some increased pinprick sensation to just above each knee. Five hours later both patellar reflexes had returned, the right more active. The patient could perceive more sensation in the right buttock. Six hours later the patellar reflexes were more active. A flicker of right quadriceps movement was noted.

Over the following hours of decompression the achilles reflexes returned, the right again more brisk. Slight plantarflextion of the right third and fourth toes was possible, and the entire right leg was not as flaccid as the left. Later the achilles reflexes disappeared, then recurred. After decompression, the patient had only slight ability to extend both thighs; all other muscle function in both lower extremities was absent. Light touch was intact to below both knees. No superficial reflexes were present.

Further treatment at the U.S. Army Tripler General Hospital, Honolulu, Hawaii, included the instillation of two milliliters of Depo-Medrol (methylprednisolone acetate) into the subarachnoid space after a lumbar puncture revealed an opening pressure, with the patient relaxed, of 210 mm HOH, a closing pressure of 190 mm HOH, and CSF protein of 134 mgm per cent. Four days later, DSF protein had fallen to 90 mgm per cent.

Twenty-four hours after initial hospitalization, motor function began to return to the right lower extremity, and within three days both patellar reflexes were quite brisk, the right being slightly more active. Over the next month, all sensation to light touch had returned to normal, and perception of pinprick was normal in all except a few spots in the perianal areas and the dermatomes of L-4, L-5, and S-1 bilaterally. Motor power in the right lower extremity was nearly normal. The left lower extremity exhibited generalized weakness in all muscle groups. Cremasteric and anal sphincter reflexes were normal, but abdominal reflexes were absent. The patient was able to walk without assistance, bending forward at the hips and dragging the left foot. Rectal function was normal; a

catheter was still required for bladder drainage. The spotty manner in which neurologic losses were regained while leaving small areas of sensory deficit adhering to no regular anatomical pattern was attributed to numerous bubbles at different vertical and transverse cord levels from T-10 distally.

Case VII (JA)

This thirty-seven year old Hawaiian male made seven dives in a five hour period, three to depths of 150-165 feet for 15 minutes, and two to the same depths for 3-5 minutes. The last two dives were made to about 120 feet for 20 minutes. The diver ran out of air during the last dive, and made a rapid ascent to the surface, when he noted immediate left chest and shoulder pain not associated with dyspnea. Over the next hour and one-half, left thigh pain and marked weakness of the left lower extremity developed.

Three hours after the last dive, the patient arrived at the Pearl Harbor Submarine Base. Examination revealed marked lower left extremity weakness, decreased perception of pinprick of the entire right lower extremity, lower anterior abdomen, and buttocks, with hyperaesthesia on the entire left lower extremity. Abdominal and left cremasteric reflexes were absent. The diver appeared incoherent and moderately disoriented.

At 150 feet of simulated depth in the chamber the deep tendon reflexes in both lower extremities became more active, and the left thigh pain had disappeared. At 165 feet the left chest and shoulder pain had diminished, but moderate tenderness was noted over the left third to sixth ribs in the anterior axillary line. Some return of strength in the left lower extremity was noted. Sensory findings were unchanged in the lower extremities, and the diver complained, for the first time, of pins and needles sensation over the entire left leg and on the instep area and great toe of the right foot.

Later there was improvement in the strength of the muscles of the left leg, and in its reflexes. All chest and shoulder pain disappeared, leaving only slight residual soreness. However, 127 minutes after reaching 165 feet, all previous pain, left leg weakness and depression of reflexes with onset of drowsiness recurred. The chamber was returned to the 165 foot level, the patient placed on a helium-oxygen breathing mixture, hypothermia instituted, and shivering responses curtailed in the manner described in the above class. Shortly after institution of these measures there was return of deep tendon reflexes, increase in left leg motor power, and decreased left chest, shoulder and thigh pain. Superficial reflexes remained absent for the duration of treatment. A brief recurrence of left chest pain was noted at the 140 foot level. Decreased sensation to pinprick was present over the right lower anterior abdomen, right buttock and leg, with relative hyperaesthesia over the same areas on the left, and the patient complained of pins and needles paraesthesia over the entire left leg. Residual muscle weakness was present in all left thigh and leg muscles.

During the remainder of the decompression the patient's condition improved. He was able to walk unaided at the 40 foot level. Bladder function became normal, and the patient became fully coherent and normally oriented. After decompression and hypothermia were terminated, examination revealed normal light touch, proprioception and vibratory sensation in the lower extremities. Pins and needles paraesthesias remained over the right foot, but had regressed on the left to just above the knee. Decreased sensation for pinprick was present on the right leg distally from the inguinal ligament anteriorally, and from the lower one-third of the right buttock posteriorly. Right leg motor power was normal. There was a trace of weakness in the left quadriceps and foot flexor groups, and marked weakness in the left hamstring group. Deep tendon reflexes were active in the lower extremities, but now more active on the left side. The patient walked with a foot drop on the left side.

One day after decompression motor power had improved markedly in the left leg, and levels of sensory loss had regressed. After one week the patient walked with a very slight left foot drop, right sided paraesthesia was unchanged, but now limited to the foot and lower one-third of the leg. No hyperaesthesia was present. The area of absent sensation to pinprick on the posterior right thigh and anterior thigh and leg was smaller. Normal sensation had returned to the anterior, medial, and lateral areas of the right thigh. A minimal trace of hamstring weakness persisted on the left, and the power of the left foot, ankle, and toe extensors was about normal. After five months very mild paraesthesias persisted at the tips of the right toes and right instep. Slight numbness was noted for brief periods in the left leg below the knee. The left foot dropped slightly after walking for two hours or more at a time.

AN ANALYTICAL DEVELOPMENT OF A DECOMPRESSION COMPUTER*

A. F. Wittenborn
TRACOR, Inc.
Austin, Texas

INTRODUCTION

This paper contains a discussion of the results of an empirical analysis of the relation between the depth of a dive, as a function of time, and the onset of symptoms of decompression sickness. The analysis has as its primary aim the development of an analytical model for describing the compression-decompression process in terms of a safe ascent criterion which can lead to a physically realizable decompression gauge or computer. It is, of course, always desirable, from a strictly scientific point of view, to attempt to devise an accurate theory based on all the available knowledge of the body processes which are involved in the compression-decompression cycle. However, it is by no means clear that the development of such a detailed theory can be carried out with presently available knowledge, and, as will become evident below, the empirical approach appears to be adequate if the primary goal is the construction of a practical gauge. A relatively simple model seems to give the correct answers whether or not the model itself is complete or even correct. An obvious drawback to an empirical approach is that the model must be used with caution if it is used for prediction, since an empirical formulation is primarily for interpolation and "hindsight."

As used here, the concept of a diver decompression gauge is that of a small, self-contained instrument worn by the diver which indicates to him at all times the depth to which he can safely ascend, and, when he has reached this depth, to so indicate this fact to him. The diver then can ascend further at a continuous rate which just holds the gauge indicator in the safe zone, or he can ascend by steps as indicated by the gauge. In general use the effects of repeated dives and irregular depth-time schedules will automatically be taken into account.

DESCRIPTION OF THE MODEL

The model for the compression-decompression process can be based on some suitable mathematical formulation, i.e., some differential equation, which has as the dependent variable a quantity which will be called exposure. One of the independent variables is evidently the time, t. The remaining independent variables will be space coordinates, the exact nature of which will depend on the coordinate system which is used for measurement in the body system. The exposure must be calculated as a function of the space and time coordinates, i.e., the differential equation must be solved, subject to whatever initial condition may exist in the system at zero time as a function of the space coordinates and subject to the conditions existing on the boundary of the system for all times greater than zero. To complete the model, the exposure or some quantity derived

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from it (e.g., an average of some sort over the space coordinates at a given time) must be formulated into a safe ascent criterion.

In order to be more specific and to establish the details of the procedure outlined in the preceding paragraph, a number of assumptions will be made. These assumptions are, in some cases, generally accepted by those familiar with decompression sickness. In other cases they are the result of an exercise of judgment to facilitate achieving the goal of devising a satisfactory gauge. They are listed below. No attempt will be made to justify them except that as a group, they produce the desired result.

1) An excess, above some critical amount, of inert gas in the body tissue is the cause of the symptoms of too little decompression following a dive, as opposed to an excess of inert gas in capillaries or larger blood vessels.

2) The body tissue is exposed to the inert gas at the surface of the capillaries in contact with the tissue, and the inert gas enters and penetrates the tissue by a diffusion process. Conditions in the capillary, therefore, represent the boundary conditions in the model.

3) The concentration of inert gas in the tissue is called the exposure and is due to the diffusion of the gas into the tissue as the diver is exposed to various pressures. On ascent this gas must diffuse out of the tissue. The exposure as defined is therefore a function of time and of distance from a capillary.

4) The time constants involved with the diffusion process in the tissue are very long compared to the time constants involved with the transport of inert gas between the lungs and capillaries. This implies, for the model, that for all practical purposes, the pressure or concentration of inert gas in the capillaries, and hence at the tissue boundary, is proportional to the partial pressure of the inert gas external to the diver at his present depth.

5) Because the layout of capillaries in the body tissue is complex, i.e., since there is no uniform pattern, a simple coordinate system of one space dimension is utilized. As will be seen, the equations so derived fit experimental data sufficiently well that an investigation utilizing a more complicated, e.g., cylindrical, coordinate system is not warranted. The implication here is that convergence and divergence effects are not of major importance, so that compression and decompression take place at the same rate.

6) The safe ascent criterion will be based on the concept of a "tissue ratio." Tissue ratio is defined as the ratio of the exposure to present absolute pressure.

On the basis of these assumptions, the model at this point is based on a specific differential equation, namely the diffusion or neat flow equation. There

are two independent variables, time and a single space dimension measuring distance from a (the nearest) capillary. The dependent variable, exposure, is the concentration of inert gas within the tissue and is a function of both time and distance from the capillary. The concentration of inert gas at the tissue boundary, i.e., in the capillary, is equal to the concentration of inert gas in the breathing mixture at the present depth. The initial value of the exposure for dives using nitrogen as the inert gas (the initial distribution of exposure for other inert gases will be discussed further below) is the uniform equilibrium distribution due to atmospheric pressure unless it has been disturbed by a previous depth-time history which the tissue has not yet "forgotten."

The exposure can be calculated for a prescribed depth-time dive schedule from the solution to the diffusion equation for time variable boundary conditions and arbitrary initial condition. Although it is not necessary, for the purposes of this paper, to dwell at length on the exact forms this solution takes when it is evaluated for a specific dive schedule, it is of interest to examine the solution in its general form in order to note some of its more important characteristics. The exposure, E, as a function of time, t, and distance, x, from a capillary is given by

$$E(x,t) = p \sum_{n=0}^{\infty} e^{-b_n^2 t/T} \cos b_n \frac{x}{\ell} \left\{ \frac{b_n}{T} \int_o^t e^{b_n^2 \lambda/T} d_b(\lambda)\, d\lambda + \frac{1}{\ell} \int_o^{\ell} E_i(x') \cos b_n \frac{x'}{\ell}\, dx' \right\}$$

where 2ℓ is the effective distance between capillaries, $d_b(t)$ is the depth of the diver as a function of time, E_i is the initial distribution of the exposure, p is the fractional concentration of inert gas,

$$b_n = \frac{(-1)^n (2n+1)\pi}{2}, \quad \text{and} \quad T = \frac{\ell^2}{D},$$

where D is the diffusion coefficient of inert gas in the body tissue. The quantities λ and x' are variables of integration and n is the index of summation. The form of the solution is evidently sufficiently complex so that it is not convenient to carry out extensive calculations manually; the calculations discussed in this paper were carried out on a digital computer. It will be noted that gas concentration has been expressed in terms of feet of water depth, so that the exposure has the dimensions of depth. To distinguish depth from exposure, the unit "footsworth" is used for exposure.

The following properties of the solution are of interest to this discussion:

1) The equations for the exposure contain a single unevaluated constant, T. This constant is determined by the diffusion coefficient of the inert gas in the tissue and the maximum effective diffusion path length. It has the physical dimensions

and significance of a time constant. In order to assure a correspondence between the equations and reality, the constant can be evaluated from experimental data.

2) The time constant will always appear in the equations for the exposure in the exponential factor $b_n^2\, t/T$. Since the solution is in the form of an infinite series, with n as the summation index, the successive terms in the series can be interpreted as representing the effect of different time constants, with the first term representing the time constant $4T/\pi^2$, the second $(4T/\pi^2)1/9$, the third $4T/\pi^2(1/25)$, etc. Each successive time constant is obtained by dividing by the square of the corresponding odd integer. The set of time constants determined in this way is an infinite set, but instead of having a continuous distribution of values as postulated in the Haldane model, the values have a defined pattern, with the greatest density near zero. In addition, the effect of each of these time constants is weighted by the coefficient of each term in the series. The strongest weight is placed on the longest time constant.

If the parameter, T, is known, E(x) can be evaluated. Some typical distributions are shown in Figure 1. The curve labeled 1 in the figure corresponds to the situation where the diver is on the bottom and has been there for a while. The curve labeled 2 can correspond to the distribution of the exposure when the diver has surfaced following a simple dive. The curve labeled 3 corresponds to a more complex dive with at least two descents and ascents within a period of say less than one hour. From curves of this type, i.e., for any possible distribution of exposure within the tissue, some property of the exposure must be found which is significant for establishing a safe ascent criterion. This can very likely be done in a number of different ways. In the present case, it is formulated in the following manner:

In any practical situation a diver will be directly concerned only with the depth to which he can safely ascend as opposed to being interested in knowledge concerning the nature of his state of exposure. What he is interested in, then, is a relation between a quantity which is derived from the exposure distribution or a tissue ratio, R, and the depth to which he can ascend, d_a. With the problem formulated in this manner, the diffusion model can be made of practical value by determining simultaneously from experimental data the time constant, T, and a safe ascent criterion derived from the exposure distribution.

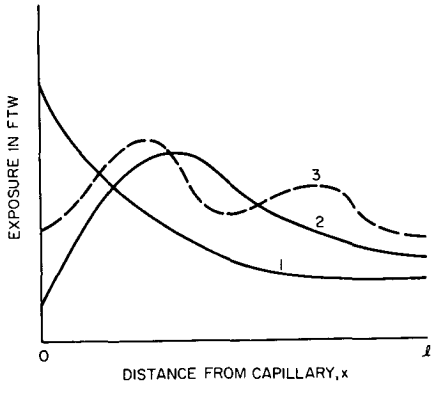

Figure 1. Three Possible Distributions of Inert Gas in the Body Tissue.

EVALUATION OF THE MODEL

An evaluation has been carried out for dives using air as the breathing mixture. The data used were those obtained by Van Der Aue, et al[1] for a series of dives requiring minimal decompression. The data cover a series of dives for which the bottom time for depths from 40 to 185 feet were determined such that the diver could just return safely to the surface without decompression stops. They were chosen because, insofar as is known, they are the most complete set available for defining the boundary between the regions in depth-time space for which decompression is or is not required. Furthermore, the data represent a set of dives of which each member should have a common property, namely that the diver can just surface safely. The curve defined by the data is shown in Figure 2. For dives of this type the distribution of exposure will have the forms shown in Figure 3 for various depth-time combinations. The relatively flat curves correspond to shallow dives of long duration while the steeper curves correspond to shorter, deeper dives.

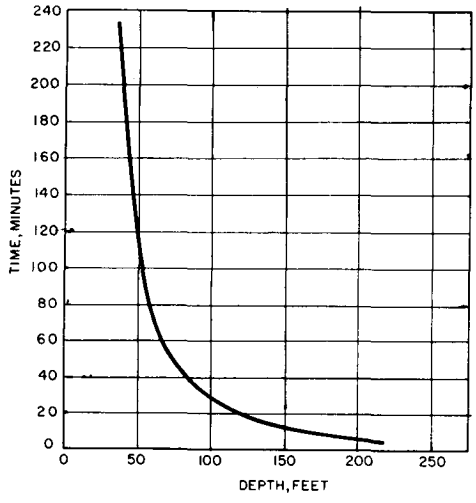

Figure 2. Experimental Minimal Decompression Curve for 75 ft/min Descent Rate and 25 ft/min Ascent Rate.

The actual evaluation of the time constant and the safe ascent criterion is, in fact, a trial and error procedure and can have a number of different outcomes. One particularly pleasing one can be described as follows (it should be remembered that this description can be given only in retrospect):

The tissue ratio, as a function of distance from the capillary, has been defined as

$$R(x,t) = \frac{E(x) + 26}{d + 33}$$

where d is present depth, 26 "footsworths" is the initial exposure due to atmospheric pressure, and 33 is the depth corresponding to absolute pressure. From physical intuition, one would not expect those regions of the tissue for which the ratio, R, is less than unity to contribute to the development of symptoms. A quantity which has been found useful is the value of R(x, t)-1, integrated over the region of tissue space in which R(x, t) is greater than unity, which corresponds physically to the quantity of inert gas contained in the region of tissue space in which R is greater than unity. This is shown schematically in Figure 4. For the minimal decompression dives, it has been found that if T is assigned the value of 900 minutes, then the integral

$$\int_a^b [R(x,t)-1]dx \approx 0.255$$

is a constant, independent of the particular depth-time combination under consideration.

Here a and b denote the limits on x between which $R(x,t) > 1$. (A value for T of 900 minutes corresponds to an RC time constant of about 360 minutes and a half-time of about 250 minutes.) The assumption is then made that the depth to which a diver can ascend, d_a, following a dive schedule other than a minimal decompression one can be computed from the relation

$$\int_a^b \left\{ \frac{E(x) + 26}{d_a + 33} - 1 \right\} dx \leq 0.255.$$

The degree to which this assumption can be justified will be considered further below.

It is of interest to consider the application of the criterion just defined to a number of dives other than the minimal decompression dives. A question of prime importance is the resolution implied in the model, i.e., what deviation in the value of the integral from the constant 0.255 is significant in the appearance of symptoms. For this purpose, three dives known as standard dives(2,3) have been investigated. These three dives are for a duration of 30 minutes at 90 feet, 110 feet and 125 feet, and no decompression stops are used. The values of the integral for these three dives are 0.258, 0.335 and 0.38 for the 90-foot, 110-foot and 125-foot dives, respectively and are shown schematically in Figure 5. The value of 0.255 for the minimal decompression dives is determined so as to represent a very conservative criterion (less than 10 out of 120 trials resulting in symptoms no worse than "post dive fatigue"). If one is willing to incur such symptoms as "rash" and "itch," the value could be increased to 0.27 or 0.28. If one is willing to incur an occasional mild case of bends, the value could be increased to 0.30 or 0.31. This response to the minimal dives corresponds to the observed response to the standard dives. Depending on the conservatism desired or on the group of individuals involved, a value for the ascent constant between 0.255 and 0.30 can be used.

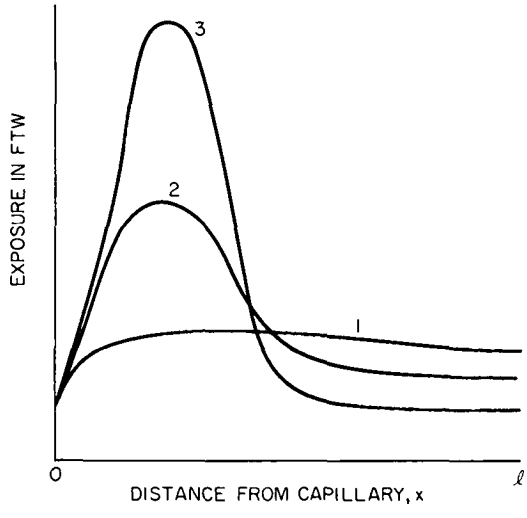

Figure 3. Typical Distributions of Exposure on Reaching the Surface after Minimal Decompression Dive for Various Depths.

A number of dives requiring decompression stops have been computed using the model. A group that has received the most attention is a set of repetitive dives, ranging in depths from 40 to 190 feet, in duration up to eight hours, and including up to three ascents and descents. The dive schedules were supplied

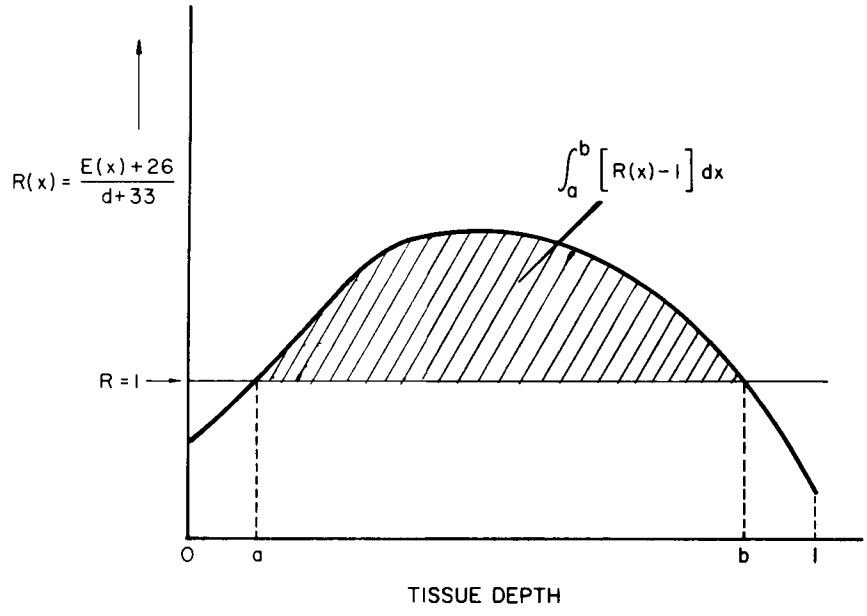

Figure 4. Graphical Representation of Threshold Criterion

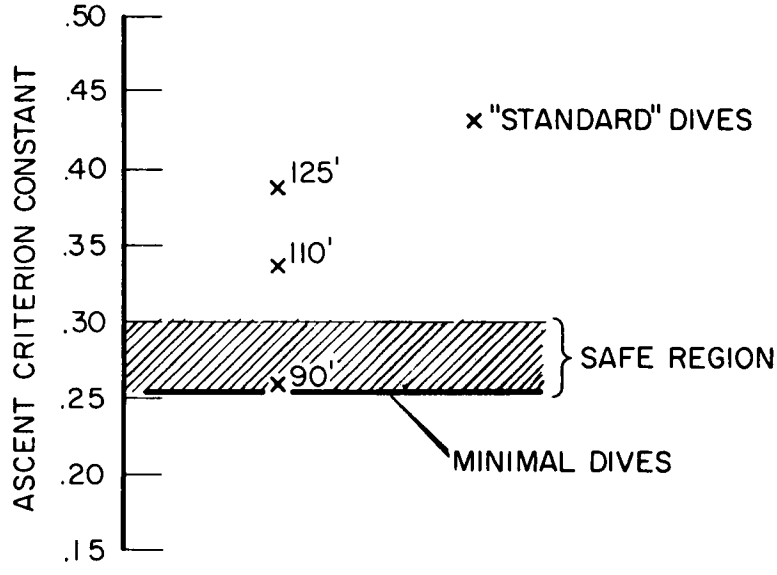

Figure 5. Resolution of the Model as Indicated by the "Standard" Dives of 30 Minutes at 90 Feet, 110 Feet and 125 Feet.

by the U.S. Navy Experimental Diving Unit, and the present model was used to determine the decompression stops when necessary. The dives were carried out experimentally at EDU with the divers subjected to their post dive altitude evaluation technique. No statistically significant deviation between the model and the experimental results has been found to date. In fact, as a result of some analysis (which will not be given here) using the model, it has been possible to predict the mean time to symptoms as measured by the altitude evaluation technique, i.e., to predict the average length of time after surfacing when symptoms will appear.

Because of the way in which the model is constructed, it can give results in keeping with an equivalent air depth concept if N_2-O_2 mixtures other than 80 per cent - 20 per cent are used. So far as is known, no conclusive statistically significant evidence exists to indicate that this concept is not valid[4]. On the other hand, if the equivalent air depth concept can be shown not to be valid, the multiplicative constant, p, can readily be reinterpreted to accommodate the experimental results.

A small amount of work has been done to examine the effect on the model of using an inert gas other than nitrogen. The use of a helium-oxygen mixture differs from the case for air in the initial condition. For air dives the tissue has been exposed to 26 feet equivalent of nitrogen pressure before the dive, while for dives using helium, the initial exposure is zero. Besides this, the two cases can also differ in values for T and the safe ascent criterion constant.

Minimal decompression dives with a breathing mixture of 80 per cent He and 20 per cent O_2 have been examined using the data obtained by Duffner, Snyder and Smith[5]. These data are not as extensive or complete as the corresponding data using air, so the study of these dives cannot be considered as reliable as that for the air dives. Nevertheless, the results are of some interest.

1) An investigation of the initial condition has shown that no consistent results can be obtained if the initial nitrogen content of the tissue is neglected. The effect of the two gases appears to be additive.

2) The best correspondence between the model and the experimental data is obtained if the value of the time constant is set equal to the value for the air dives and the safe ascent criterion constant is increased slightly. The higher value for the criterion constant can imply a higher tolerance level of the body to helium[6]. These two items bring up some interesting speculative points. Since the time constant is the same for the two gases (and hence the diffusion coefficient if the diffusion length has not changed), one can conjecture that neither of the two gases is actually involved in the production of decompression sickness. Since it is known that breathing He mixtures lowers the concentration of retained CO_2 in the body which accounts for the apparent higher tolerance level of the body to helium, one can conjecture further that decompression is, in fact, controlled by CO_2. The importance of the inert gas arises from its physiological effects outside of decompression sickness and from its effect on CO_2 retention.

The actual construction of a decompression gauge based on the model described above can be carried out in a number of different ways. The diffusion equation is the equation which governs a number of different phenomena. Besides diffusion itself, it describes heat flow and the behavior of an electrical transmission line which does not contain any inductance. By analogy to the transmission line, the same equation also describes (a) the flow of fluid in a hydraulic system consisting of tubes and bellows in which the mass of fluid can be neglected and (b) the movement of springs and mechanical resistances (dashpots) of small mass. Several different versions of the gauge have been constructed or are in the process of being constructed. One of the earlier models is presently being tested at the Experimental Diving Unit.

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SECOND SESSION
PREVENTION AND TREATMENT OF BENDS

H. F. Alvis, Chairman

ALVIS: I would like to start the discussion by asking members of the Panel if they would care to ask questions of each other.

ERDE: Dr. Mackay mentioned that the Royal Air Force has been reluctant until recently to employ hyperbaric treatment in cases of decompression sickness incurred in flying. This is true also in aviation in the United States but the situation is now changing.

MACKAY (D): I agree. It is changing in Britain as well.

ALVIS: There is still another kind of bends problem related to aviation. This is the initiation of bends in divers by ascent to altitude following ordinarily safe decompression from a dive. In the Pacific our Air Force has gone to the extreme of requiring that aviators to not engage in SCUBA diving for a period of at least 12 hours preceding any flight. The waters of the Pacific offer enticing sport and many of the aviators are enthusiastic SCUBA divers. Military fliers are told to get their diving done before noon on Sunday if they are to fly on Monday. It now seems that the U.S. Air force is now obtaining positive pressure chambers for treatment of inflight dysbarism.

Dr. Mackay made reference to the repetition of the long Table. When the first use of the long Table, that is Table 3 or 4, has failed to produce a cure, do you feel it is worthwhile to repeat the treatment?

MACKAY (D): Yes, I do. This approach has been successful. I would use it when the treatment has apparently been successful but the symptoms recur.

ERDE: I personally haven't been very impressed with our gains in repeating a treatment schedule with the long treatment tables. We have found that if the patient does not improve on compression and you put him back for a second treatment and even sometimes for a third, you don't know if any benefit is due to your treatment or just the tremendous number of hours which have elapsed since exposure.

MACKAY (D): The problem is with the patient who apparently recovers then appears to deteriorate for some reason.

ALVIS: You are speaking about what we would call a recurrence. I think that we would all agree that recurrence of bends requires retreatment. What to do with a patient who still has disability at the end of the pressure treatment or whose disability is possibly worse is a more difficult problem.

Do any of you relate the seriousness of decompression sickness to the nature of symptoms? When you say a serious case of the bends, do you mean

a case of decompression sickness which is difficult to treat or do you mean one in which the symptoms that the subject has are severe?

MACKAY (D): I think that the ache which clears when one uses therapeutic Table 1, is a much milder condition than that of the shocked patient. The patient's reaction defines the seriousness of bends.

ALVIS: Then you feel it is the same disease and the same mechanism, differing only in the severity of the symptoms?

ERDE: I would like to answer that in two ways. Based primarily on the symptoms, the man who gets immediate relief from such bends reactions as pain only or pain and skin rash would not be considered to have a serious "hit." But if he had pulmonary or nervous system involvement, then this would indicate a serious category of bends. However, there are exceptions where men with serious symptoms have had a complete clearing of all their symptoms in an hour or two subsequent to surfacing and then will have a recurrence. Others, who have had very minimal symptoms will develop very serious effects after a period of time has elapsed, whether they are in the treatment chamber or waiting in the treatment facility. Serious bends can develop in a man who initially presents no or very minimal symptoms. You will have to say that foresight is better than hindsight by a damned sight but it is a little hard to count on all the time.

BARTHELEMY: I don't think that either the number or size of the bubbles is proportional to the gravity of the bends. Nervous phenomena that intervene also relate to bubble formation. There are a lot of reflex mechanisms involved in the symptomatology of bends. Nervous and endocrine factors affect the sympathetic and parasympathetic mechanisms relating to vasocilatation and vasoconstriction and therefore, alter circulation.

WOOD: Dr. Rivera has analyzed about 1000 cases of bends occurring in or reported to the Experimental Diving Unit(1). I had the privilege of reading this analysis and I think that the over-all results of treatment are a little better than Mackay has reported. Our Table 4 treatment though does appear to leave a great deal to be desired. I wonder if Dr. Rivera would care to summarize for us some of these reports?

RIVERA: Of the 935 cases of bends reported to the Experimental Diving Unit in the past 15 years, 888 were treated according to the standard procedures of the U.S. Navy Treatment Tables and are therefore subject to valid comparison. Seven hundred seventy-three patients of this number were relieved on initial treatment. One hundred fifteen others represented failure of initial treatment due either to the separate problems of residual symptoms or of recurrence of the bends. Eighty-six patients in the failure group were subsequently retreated and 70 were relieved. In summary, then, of 888 cases treated 843 patients were eventually relieved. There were 45 failures of treatment, although valid reasons for failure not related to the Treatment Tables themselves could be pointed out in 30 cases. The 15 cases of "true failure" of the Navy Treatment Tables represent 1.7 per cent of all patients treated.

If results of the individual tables are considered, Tables 1, 2, and 3 all had an initial failure rate of about 6 per cent no matter whether air or oxygen was used in the table. Failures from Tables 1 and 2 did better on retreatment than did initial failures with Table 3. All the 15 cases of "true failure" mentioned previously came from Tables 3 and 4. Table 4 patients had the worst rate of failure (25 per cent) on initial treatment. Since most of the failures were due to residual damage rather than recurrence, the situation was not altered much by retreatment. One must remember, however, that these patients were given the most extensive treatment initially because they were the most seriously ill when first seen.

VAN DER AUE: I think we had failure on Table 4 because we had permanent damage. You cannot treat the tissue damage, hemorrhage or edema directly with decompression therapy. The signs and symptoms of damage may persist in a severe case.

AQUADRO: These serious cases that necessitate treatment on Table 3 or 4 probably do have much more tissue damage to deal with. However, in any case of decompression sickness the primary treatment is recompression. In addition, we have heard of two adjunctive therapies; the administration of heparin by French investigators and hypothermia as used by Dr. Erde. What does the Panel think about the use of urevert solution, urea or invert sugar as adjunctive therapy to reduce cerebral edema?

ERDE: There are other ways of treating cerebral edema. We assume that edema occurs in nervous tissue everytime it is insulted to the point where there are functional losses. Hypertonic solutions which have been tried include mannitol, urea, invert sugar and glucose. I don't know of any well controlled study which shows these to be effective in diving casualties, but they have been shown to be helpful in neurosurgery to reduce brain bulk. They work there, and I assume that they will work just as well in decompression sickness as in the other applications where edema is a problem.

BARTHELEMY: We have tried hypertonic glucose in two cases of air embolism in which all other treatments were tried without beneficial results. In one case we got a spectacular success; in the other case there was no definite improvement. We then tried heparin on this last case, and there was good recovery. We cannot say whether this was due to the hypertonic solution, or to the heparin that was later used, with its effect on cerebral circulation.

ERDE: Hypertonic solutions such as urea will help resolve the edema. Hypothermia has several additional advantages. It will not only help the edema itself but it will protect the tissue from some of the adverse effects of hypoxia.

GILLEN: One study on spinal cord edema and treatment was reported at the Academy of Neurology in April of 1962. Fortunately for better comparison with practical diving problems, the investigators waited to begin treatment. It was discovered that a lesion which, as a consequence of edema, had progressed from swelling, to the point of parathesia, could still be successfuly treated with urevert, provided they waited no longer than six hours. They were not successful

if the lesion was tissue destructive. If they waited beyond about six hours they were not able to significantly modify the cord pathology in any case. This procedure, as an adjunct to recompression, may afford some relief for the small circumscribed lesion of the sort that we find in the cord after bad diving technique. I would like to support Dr. Erde in the use of hypothermia with recompression because I think this can be a very good procedure also. I definitely would not like to support the use of hypothermia to the exclusion of recompression, as has recently been described by the American Association of Orthopedic Surgeons at Miami Beach. There is a physician in Toronto who has treated bends among the tunnel workers with ice packs only. He says he can get very good relief in 12 hours on ice and most of his patients were symptom free in 10 to 12 days. This, without recompression, is not the type of treatment we would like to recommend.

LANPHIER: I think it is an extremely healthy and encouraging thing that our time-honored program for treating decompression sickness is being questioned and I am particularly interested in the possible importance of edema. It is apparently a common thing for a patient to be treated on Table 3 or Table 4 and get worse some hours later as he is being brought up. We do not have adequate information to know whether most of these cases represent development of edema after a delay or represent reformation of symptomatic gas bubbles. Until we know this, I hope that it will not be assumed that this is always edema. That would lead to failure to retreat some treatable lesions. I also would like to speak in favor of the cookbook approach. I have never felt that I had a legitimate basis for making any very large modification in the established treatment procedure.

LAMBERTSEN: Dr. Alvis, I think that it has been very well expressed that treatment of the bends, mild or severe, requires recompression chambers. It is also true, though, that there are times when large recompression chambers, or any chambers, are not immediately available. We should discuss what may be considered a rational preliminary treatment of decompression sickness, either while waiting for the patient to arrive at the compression chamber, or when it is absolutely impossible to ever use a recompression chamber. Hypothermia was mentioned, but the approaches to reducing body temperature did not seem adequate for the possibly great gains. I would like also to point to the great advantages of immediate initiation of pure oxygen breathing at sea level as a means of oxygenating tissue and eliminating inert gas from bubbles and cells. This hasn't been raised as yet. Could we have discussion of the possible advantages of these approaches to bends therapy? It is also worth discussing how small transportable pressure chambers may be most effectively used.

ALVIS: We have in Hawaii developed recommendations to be followed when a chamber is not available. They are:

1. Do not put the patient back in the water for decompression.
2. Give oxygen by mask.
3. Arrange air transportation to cut down on travel time; but the plane should fly at the lowest level concomitant with flying safety.
4. Communicate ahead to arrange for treatment.

I believe these are the points that Dr. Lambertsen wishes to have made here. There are indeed things that can be done if it is possible to transport the patient to adequate treatment. If it is utterly impossible to move the patient to a recompression chamber within a reasonable period of time, then I would be inclined to give oxygen continuously by mask and, if neurological symptoms were involved to use hypothermia as well. Hypothermia means actual reduction of body temperature, not just local relief of pain by ice pack.

MACKAY (D): We have been confronted with the preliminary treatment problem as the result of treating civilian divers at our naval facilities. We place fairly strong emphasis on the lowering of metabolism as much as possible. Sedation is recommended as well as hypothermia. Recently we attempted treatment of bends in two men by using oxygen alone, rather than recompression. These were men with limb aches who asked if they could rather have aspirin and stay out of the chamber. They were given oxygen for 30 minutes and were closely followed for any change of physical condition. They had no improvement with oxygen and had to be treated on Table 2 in the recompression chamber. I would not be happy using oxygen alone. The treatment for bends is still recompression.

BARTHELEMY: I personally don't think any drug such as adrenalin should be given before the patient is brought to the chamber. This happens frequently before we see the patient. We believe that patients given adrenalin deteriorate much more rapidly prior to recompression.

BORNMANN: There are times, as when the severe hypotension of shock exists, when use of a vasoconstrictor may be necessary.

ALVIS: I must comment further about the rationale of not putting the patient back into the water for decompression. Objection to this is based on the premise that he must ultimately be transported to a chamber. If he is put back into the water it amounts to having added one more dive to an already atrocious accumulated diving history.

I am disappointed that we have had no questions of blood sludging in relation to blood viscosity, or questions about the digital computer approach to decompression.

MACKAY (S): One comment about the computer approach is that we are really concerned with two computers. One form of computer warns a diver when to terminate his dive; the other indicates how to decompress.

ALVIS: It is unfortunate that we must end this discussion of bends prevention and treatment without further attention to the details of computer implications, the aspects of blood sludging and viscosity, the use of drugs for supportive purposes and the very important problem of communicating information regarding improvements in therapy

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RESPIRATORY RESISTANCE WITH HYPERBARIC GAS MIXTURES

A.A. Buhlmann
Director, Cardio-Pulmonary Laboratory
Kantonspittal, University of Zurich
Zurich, Switzerland

METHODS

These experiments, involving resistance to breathing at high ambient pressure, were made upon eleven normal, male volunteers (Table I). The subjects were exposed to positive pressure in a dry gas chamber. The effects of several gas mixtures were studied, as follows:

	Mixture	Used at pressure to
Helium	90 ± 3%, balance oxygen	30 kg/sq cm (9.7 atm)
Nitrogen	90 ± 3%, balance oxygen	15 kg/sq cm (19.4 atm)
Argon	90 ± 3%, balance oxygen	10 kg/sq cm (29.0 atm)

Each subject was tested twice under each experimental condition.

Figure 1 shows the arrangement of apparatus. An esophageal tube ending in a balloon 10 cm in length was placed in the esophagus through the nose. Esophageal pressures were measured with Statham strain gauges, Model P6 ± 3D-350, having a pressure range of ± 3 psi. This tube was connected to the strain gauge only during conditions of constant pressure, and not during ascent or decompression.

The pressure in the chamber was raised by compressed air. The individuals being studied breathed this chamber air up to a pressure of 10 kg/sq cm (9.7 atm); at this pressure the breathing mixture was changed to 90 per cent helium with oxygen, administered through a demand valve and mouthpiece for further increase in pressure.

Two types of Fleisch pneumotachographs were used to measure ventilatory flow rates. The first was for flow rates up to 2500 ml/sec and the second for higher flow rates. The pneumotachographs were calibrated with air and corrections were made for the effect of the change in viscosity when used with the helium-oxygen and argon-oxygen mixtures. Pneumotachograph pressures were registered with a Statham strain gauge having a pressure range of ± 0.05 psi.

Test gases were administered from a collapsible bag within the chamber. At the various test depths, the subject breathed first the helium-oxygen, then the nitrogen-oxygen and finally the argon-oxygen mixture. These gas mixtures were changed by the operator outside the chamber The gas bag was flushed several times with each new gas mixture by the investigator ("control person") in the chamber. The recording period was begun after the subject had taken several deep inhalations and exhalations to replace the gas in his lungs with the new mixture. After normal, spontaneous breathing had been recorded, periods of deep respiration

TABLE I

Subject	Age (yrs)	Height (cm)	Vital capacity (ml)	Timed vital capacity, 1 sec (% v. c.)
EM	20	174	4800	86
HN	20	176	5200	87
PW	22	183	6200	80
MS	22	174	4800	87
IS	24	172	4700	87
FB	26	172	4800	75
AG	23	175	5600	87
EF	22	164	4500	79
HK	27	174	4900	80
IG	24	171	4750	74
FC	23	175	4900	89

and of rapid respiration were carried out under instructions given through the loudspeaker system. The total time required for recordings on the three gas mixtures was between three and four minutes.

The resistance to gas flow was estimated by the formula

$$\text{Resistance} = \frac{\text{Pressure}}{\text{Flow}}$$

where pressure is the resistive pressure, $P_{(RES)}$, obtained from the relationship

$$P_{(RES)} = P_{(ESOPH)} - P_{(EL)}$$

$P_{(ESOPH)}$ is the total esophagael pressure and $P_{(EL)}$ is the component of esophageal pressure obtained as follows. The linear connection of the points of zero flow between inspiration and expiration gives values of $P_{(EL)}$ for every

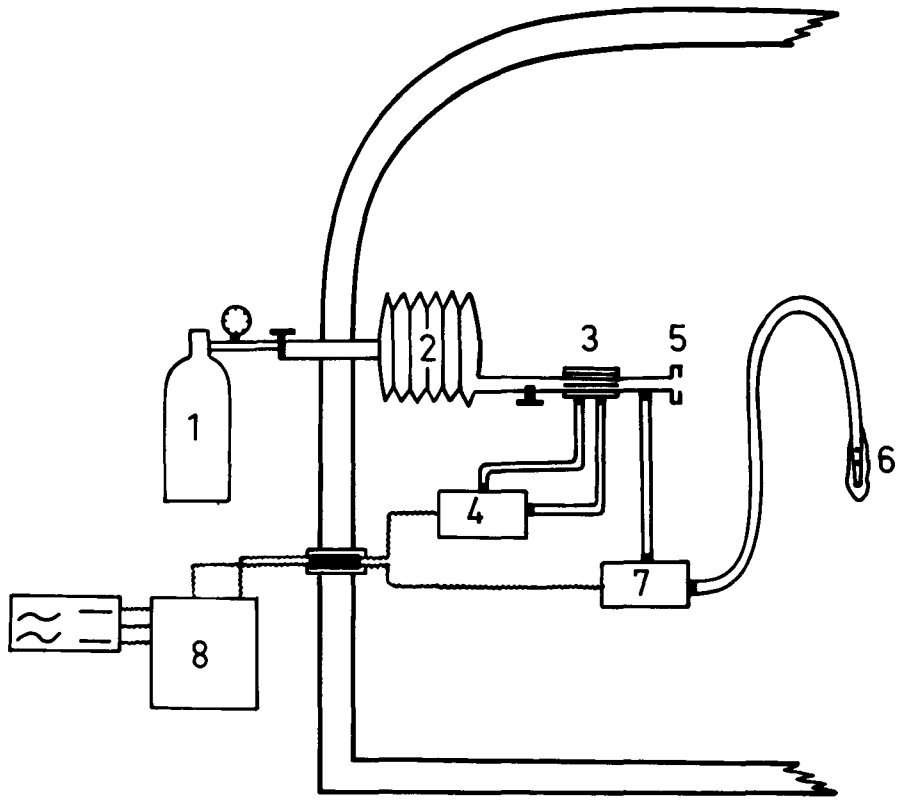

Figure 1. Set up of the Instruments. 1, bottle with the gas mixtures outside the pressure chamber; 8, amplifier and recorder of the strain gauges (4 and 7); 2, bag with no return; 3, pneumotachograph; 5, mouth piece; 6, esophagus tube with balloon; 4, strain gauge for the pneumotachograph; 7, strain gauge for the esophagus pressure (pressure difference against mouth pressure for compensation of the resistance of the pneumotachograph).

point during inspiration and expiration (Figure 2). The difference between the esophageal pressure and this line gives the deviation of resistive pressure. Respiratory work was determined by integration of pressure and volume. A total of approximately 550 single values were utilized in this study.

GENERAL ASPECTS

The units of pressure calculation employed were:

$$1 \text{ kg/sq cm} = 10 \text{ meters } H_2O$$

$$10 \text{ meters} = 32.8 \text{ feet}$$

A comparison with hydrogen of the molecular weights and densities of the gases used is as follows:

	Molecular weight	Density relative to hydrogen
Hydrogen	2	1
Helium	2	2
Nitrogen	28	14
Oxygen	32	16
Argon	39.9	19.8

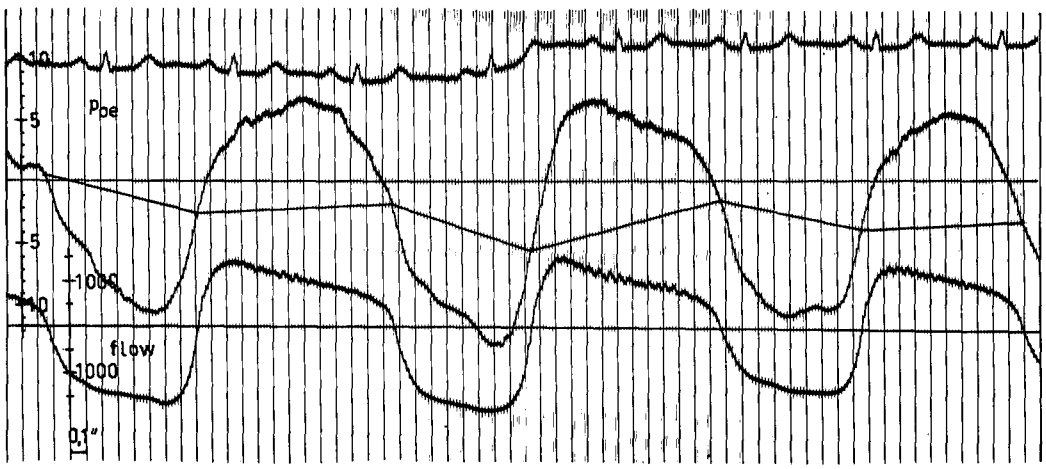

Figure 2. Original Curve of Esophagus Pressure and Flow at 10 kg/sq sm Breathing 90% Nitrogen. Linear connection of the points of zero flow between inspiration and expiration. The difference of esophagus pressure and this line gives P_{alv}.

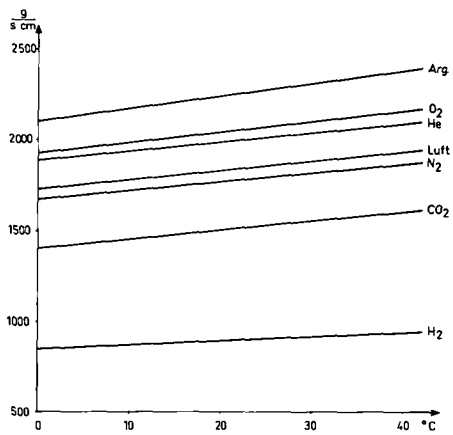

Figure 3. Dynamic Viscosity of some Gases at Different Temperatures (Poise = gm/cm sec).

It can be shown that the relation between flow and resistive pressure is non-linear (Figure 4). Alveolar pressure represents the summation of pressure influences resulting from laminar and turbulent flow effects. Thus,

$$P_{alveolar} = P_{laminar} + P_{turbulent}$$

In this expression $P_{laminar} = \dot{V} \cdot K_1$ where K_1 is the Hagen-Poiseuille constant.

$\dot{V}$ = flow

$K_1 = \frac{8\ell\eta}{\pi r^4}$

η = dynamic viscosity

Thus, $P_{laminar}$ is directly proportional to the flow rate and to the dynamic viscosity of the gas.

$$P_{turbulent} = \dot{V}^2 \cdot K_2$$

$$K_2 = \delta \cdot k \cdot a$$

where δ is the gas density and k and a are constants related to the geometric form of the tube. Therefore, $P_{turbulent}$ is directly proportional to the square of the flow and to the density of the gas[1].

The viscance value, $(P_{alv})/\dot{V}$, is linear in this form and a square component. Reynold's number is related to the geometric form of the airway, depending on whether the space flow is laminar or turbulent.

$$\text{Reynold's number} = \frac{v \cdot d \cdot \delta}{\eta}$$

v = velocity of gas

d = diameter of tube

This equation shows that turbulence is increased by high velocity and high density, whereas a high viscosity diminishes Reynold's number if the diameter is constant. Therefore the initiation of turbulence occurs at a higher gas velocity when viscosity is increased. At 37° C the dynamic viscosity of 10 per cent helium in oxygen and that of 30 per cent argon in oxygen are higher than that of air. In regions of predominantly laminar flow and with flows up to approximately 1000 ml/sec., an increase of flow resistance can be expected of 10 to 12 per cent with the helium-oxygen mixture and 25 to 27 per cent with the argon-oxygen mixture. As a result of this factor, an increased resistance to gas flow can be expected as the ambient pressure is raised, for all gas mixtures except hydrogen. In regions of predominantly turbulent flow, the breathing resistance with a helium-oxygen mixture should increase less than with nitrogen-oxygen mixtures.

When breathing argon-oxygen mixtures, very high values for resistance are found as a consequence of a high density and viscosity.

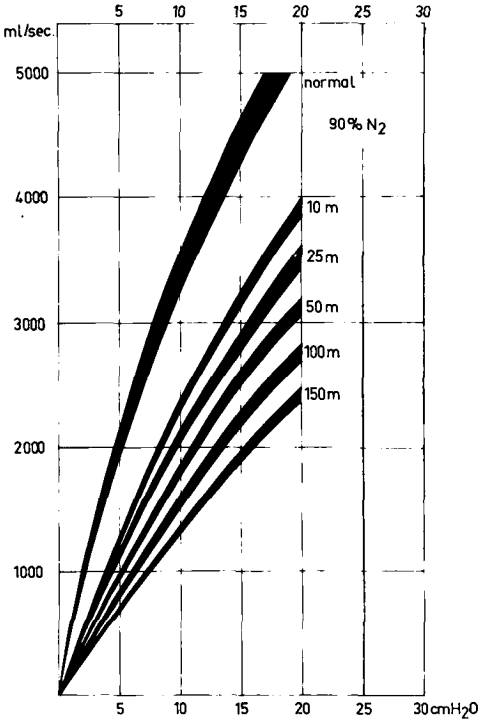

Figure 4. Airway Resistance Breathing 90 ± 3% N_2 at Different Pressures in Relation to the Normal Values at the Surface Breathing Air. (Normal values from Mead and Whittenberger 1954 and Rossier and Buhlmann 1959).

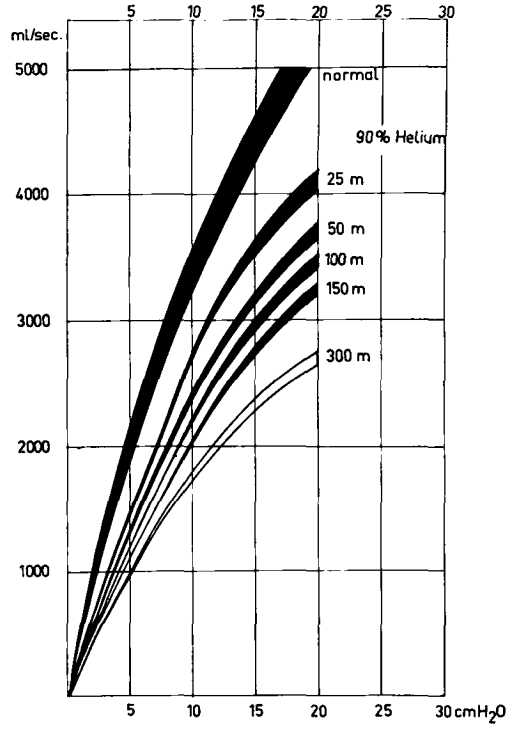

Figure 5. Airway Resistance Breathing 90 ± 3% He at Different Pressures in Relation to the Normal Values at the Surface Breathing Air. (300 m data from 2 individuals).

RESULTS

Figures 4, 5 and 6 illustrate the mean values found with the three gas mixtures at the various conditions of pressure (water depths in meters) in relation to the normal values observed breathing air at normal pressure. The curves were obtained from the data of Table II, using additional values such as 1500, 2500 and 3500 ml/sec. All values are rounded to whole numbers. Only one value in Table II demonstrates identical results in different experiments. As can be seen from Table II, the scatter of values is greater than the width of the semi-diagrammatic curves. The mean values shown are for inspiration and exhalation respectively, at the mid-point of lung filling. At the end of expiration significantly higher values are often registered as a result of bronchiolar compression by the high alveolar pressure. Figure 7 demonstrates the viscance during inspiration and expiration breathing the helium and the nitrogen mixtures at a positive ambient pressure of 10 kg/sq cm (9.7 atm). At the end of expiration the flow

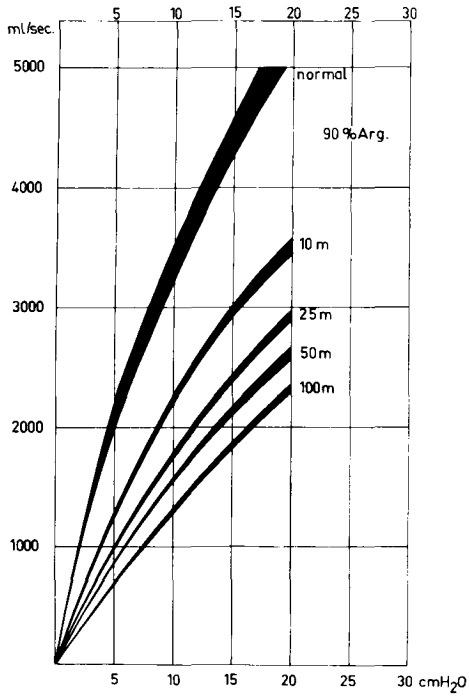

Figure 6. Airway Resistance Breathing 90 ± 3% Argon at Different Pressures in Relation to the Normal Values at the Surface Breathing Air.

resistance increases markedly, especially with the nitrogen-oxygen mixture.

Marshall and co-workers[2] found in three subjects breathing air at 99 feet (3.0 kg/sq cm or 30 m) a flow resistance twice as high as at the surface. Our results agree with these findings as far as they can be compared. The behavior of the airway resistance corresponds to the theoretical expectations. Figure 8 shows the starting point of turbulence for various gases in relationship to increased ambient pressure at the given flow rate and diameter. With increasing flow rate the starting point for turbulence is displaced to the left. There is a significant difference between the curves calculated for helium and hydrogen and those found with argon and nitrogen.

As a consequence of the increasing flow resistance the respiratory work becomes greater and reaches extremely high values at great depths with high ventilation rates. Table II shows respiratory work against viscous resistance breathing the various gas mixtures at three different ventilation rates. A respiratory work rate of more than 6 to 7 kg-m is felt to be very strenuous and uncomfortable. Breathing air or a nitrogen-oxygen mixture thus reduces the ventilation to 30 to 40 l/min at an ambient pressure of 10 kg/sq cm or breathing an argon-oxygen mixture at a pressure of 5 kg/sq cm. As far as practical diving is concerned the additional resistance in the tubes and valves of the diving equipment has to be taken into account. These increase the total respiratory resistance and hence the total respiratory work.

According to the high values of vital capacity (Table I), all test persons had low values for elastance, between 3 and 4 cm H_2O/l. As a result of uneven gas distribution, probably related to increased airway resistance, a variation of the elastance in patients with bronchial obstruction was found. However, a doubling of the elastance, when contrasted to the increased flow resistance, plays a minor role in the total respiratory work.

TABLE II

Respiratory Work (kg-m/min) (mean values)

Ventilation 10 000 ml/min, Respiratory rate 15.1, Tidal volume 660 ml			
Pressure (kg/sq cm)	90% Helium	90% Nitrogen	90% Argon (± 3%)
surface	(0.21)	0.19-0.20	0.22
1	(0.21)	0.24	0.26
2.5	0.20	0.26	0.41
5.0	0.21	0.29	0.48
10.0	0.22	0.32	0.55
15.0	0.27	0.37	
30.0	0.38		
Ventilation 30 000 ml/min, Respiratory rate 25.0, Tidal volume 1200 ml			
surface	(1.6)	1.8	2.5
1	(1.8)	2.1	2.3
2.5	1.85	2.4	3.9
5.0	2.0	2.7	4.6
10.0	2.1	3.2	5.2
15.0	2.6	4.0	
30.0	3.6		
Ventilation 50 000 ml/min, Respiratory rate 35.0, Tidal volume 1430 ml			
surface	(4.5)	5.0	6.5
1	(5.2)	6.5	7.9
2.5	5.9	8.6	11.1
5.0	6.7	9.5	12.7
10.0	7.6	10.7	17.0
15.0	8.7	13.0	
30.0	11.3		

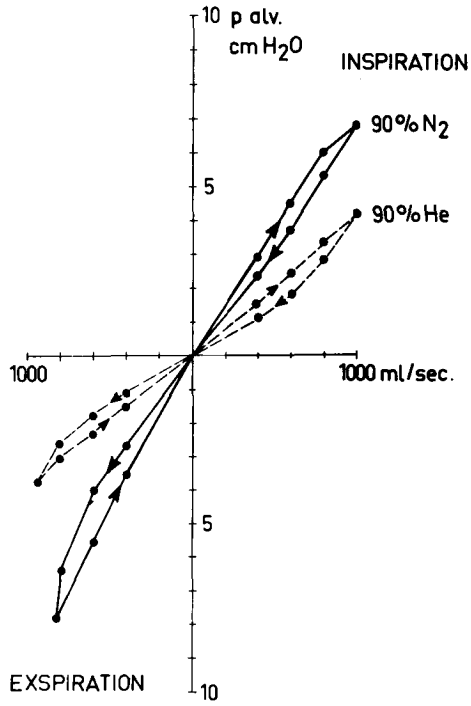

Figure 7. The Changing Viscance During Inspiration and Expiration, Breathing N_2 and He at 10 kg/sq cm Ambient Pressure.

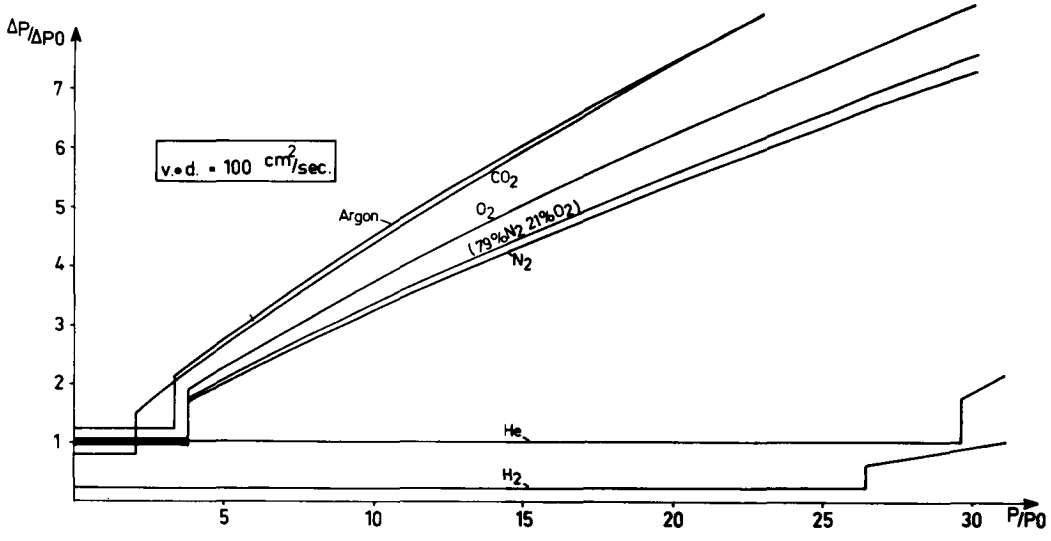

Figure 8. The Starting Point of Turbulence Breathing Various Gases in Relation to Pressure for a Given Flow of 360 ml/sec and a Diameter of 20 mm (v·d = 100 sq cm/sec). P/P_O = relationship of total pressure to normal pressure. Ordinate = resistive pressure.

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VENTILATORY DYNAMICS UNDER HYPERBARIC STATES

W. B. Wood
Department of Internal Medicine
School of Medicine
University of North Carolina
Chapel Hill, North Carolina

Deep sea divers recognize a reduced ability to hyperventilate at several atmospheres ambient pressure. While this reduction in ventilatory capacity at increased ambient pressure has often been discussed, there have been only limited reports of actual physiological observations.

Rohrer's equation, $P = K_1(\dot{V}) + K_2(\dot{V})^2$, is most commonly accepted as representing the conditions for physiological gas flow at one atmosphere absolute pressure. K_1, the constant for laminar flow, is viscosity dependent; K_2, the constant for turbulent flow, is density dependent. The predominant flow pattern in the respiratory passages was originally presumed to be laminar; turbulent flow was thought to exist only at points of cross sectional change and normal anatomical airway irregularities. This assumption was probably erroneously drawn due to incorrect evaluation of air flow velocity[1].

Because of the need for deep diving operations by the U. S. Navy and the need for heavy work during such dives, it is important to know the limitations imposed upon and by the human respiratory apparatus. We have little information on the effects of air or helium on the ventilatory dynamics below 200 feet and scant comparison of the various gas media in the shallower depths. Miles[2] reported mean percentage reduction in maximum breathing capacity of 52% at 200 feet sea water equivalent depth, breathing air. No measurement of flow rates was made and there was no comparison with helium-oxygen mixtures. Marshall, Lanphier and DuBois[3] found a linear decrease in the maximum expiratory flow rate with increasing depth.

METHOD

In this study, which was carried out by the U. S. Navy Experimental Diving Unit, maximum breathing capacity (MBC), timed vital capacity (TVC), and maximum sustained expiratory flow rates (MEF) were performed by eleven male subjects using a low resistance, 13.5 liter Collins Respirometer installed in a U. S. Navy recompression chamber. Resistance to air flow in the respirometer tubing measured 0.12 cm $H_2O/L/sec$ at one atmosphere absolute and increased to 0.20 cm $H_2O/L/sec$ at six atmospheres absolute.

The MBC and the timed vital capacity were performed in the standard manner. The maximum sustained expiratory flow rate was calculated from the expiratory flow curve.

PROCEDURE

The subjects were selected on the basis of normal pulmonary function (Table I). The comparative tests were conducted in five phases, which were

TABLE I

Vital Statistics of Subjects used in This Study*

	Mean	± S.D.
Age (yrs)	32.8	3.5
Height (in)	69.7	2.3
(cm)	177.1	6.0
Weight (lbs)	169	20
Body Surface Area (sq m)	1.93	0.19

*N - 11

basically the same. At one atmosphere duplicate measurements of MBC, TVC and MEF were made with the subject breathing air. The lungs were washed out with helium-oxygen for a minimum of seventy-five seconds, and then the measurements were repeated using the helium-oxygen mixture. The chamber was then pressurized at 3 to 5 atmospheres per minute and measurements were then obtained at each selected level of increase in barometric pressure.

At the extremes of positive pressure studied, a change in procedure was necessary to prevent the occurrence of nitrogen narcosis; during pressurization both the subject and investigator breathed a He_2-O_2 mixture by open circuit demand systems. In the final study, the oxygen percentage was reduced from 20% to 5% for measurement at 15 atm absolute. This necessitated a switch from the 80%-20% He_2-O_2 mixture outside the chamber at a pressure of approximately 9 atm.

RESULTS

There was a reduction in all ventilatory parameters measured with increasing barometric pressure. Table II shows the mean performances for the group at one atmosphere absolute with air and with He_2-O_2 (80%-20%) as the respiratory media. The group was normal or greater on all parameters of dynamic pulmonary function.

Figure 1 is a reproduction of a representative subject's performance. The MBC tracing on the left shows a reduction of total volume of gas exhaled, a progressive change from rapid shallow breaths to a slower respiration, and a slight change in tidal volume. The right side of the figure shows a flattening of the timed expiratory curve to an obstructive pattern with increasing pressure.

There was a progressive reduction in the actual measured MBC with increasing barometric pressure. Figure 2 gives a comparison of the percentage decrease in the MBC with air and helium-oxygen. The measurement at one atmosphere was considered to be 100% performance, i.e., no reduction. The

TABLE II

Measurements of Base Line Ventilatory Dynamics
Conducted at Surface with Collins 13.5 Liter Respirometer*#

	Mean	±S.D.
Predicted Surface MBC (L/min)	134.4	8.4
Measured Surface MBC (L/min)		
Air	180.1	27.8
HeO_2 (80% - 20%)	228.4	36.0
Predicted Surface Vital Capacity (cc)	4246	118
Measured Surface Vital Capacity (cc)		
Air	4240	487
HeO_2 (80% - 20%)	4240	485
Measured Surface MEF (L/min)		
Air	420.6	54.6
HeO_2 (80% - 20%)	548.4	76.8

Measured Surface TVC (%)

	Air		HeO_2 (80%-20%)	
	Mean	±S.D.	Mean	±S.D.
1 second	81.2	6.8	85.0	5.8
2 seconds	92.3	3.6	93.7	3.4
3 seconds	96.4	2.1	97.0	2.2

*N = 11

#Baldwin, Cournand and Richards: Medicine 27:243, 1948

rapid decrease in ventilatory performance is apparent in the moderate range to 6 atmospheres. Surprisingly, the percentage decrease in MBC even with helium-oxygen is also very striking. Studies at 15 atmospheres with the oxygen fraction in the helium mixture reduced to 5% improved the performance very significantly.

A comparison was made of the percentages of predicted MBC, Figure 3 (predicted normal here means the average normal values for the general population). The mean MBC for the subject group at 1 atm was 135% of the predicted normal value on air and 170% of predicted normal when helium-oxygen was breathed. At 2 atm the group mean was reduced to 100% of the predicted normal for air but remained well above predicted normal on helium (132%). Only when the pressure had been increased to 6 atm did the values on helium fall below the

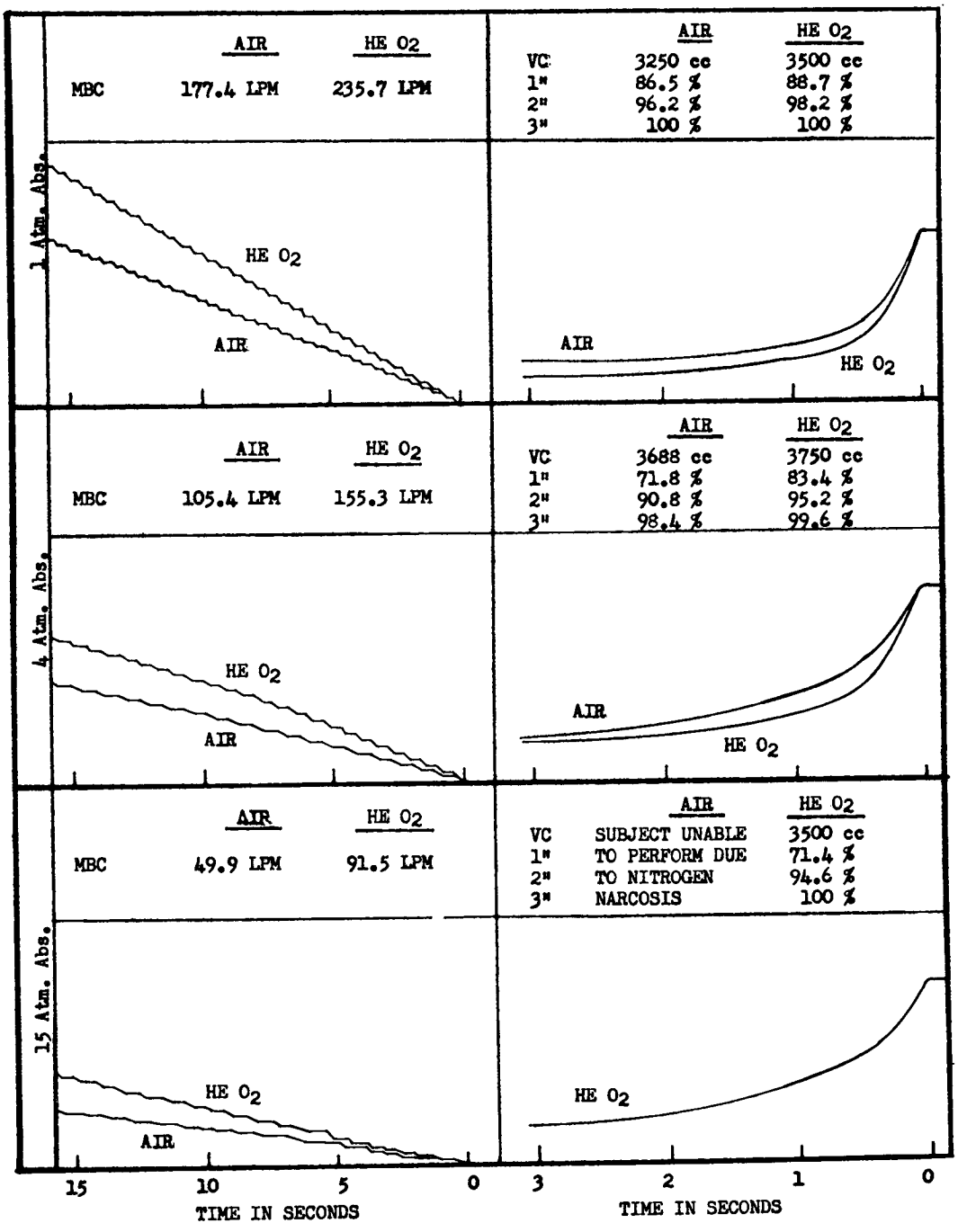

Figure 1. Representative Tracings Subject: D E K

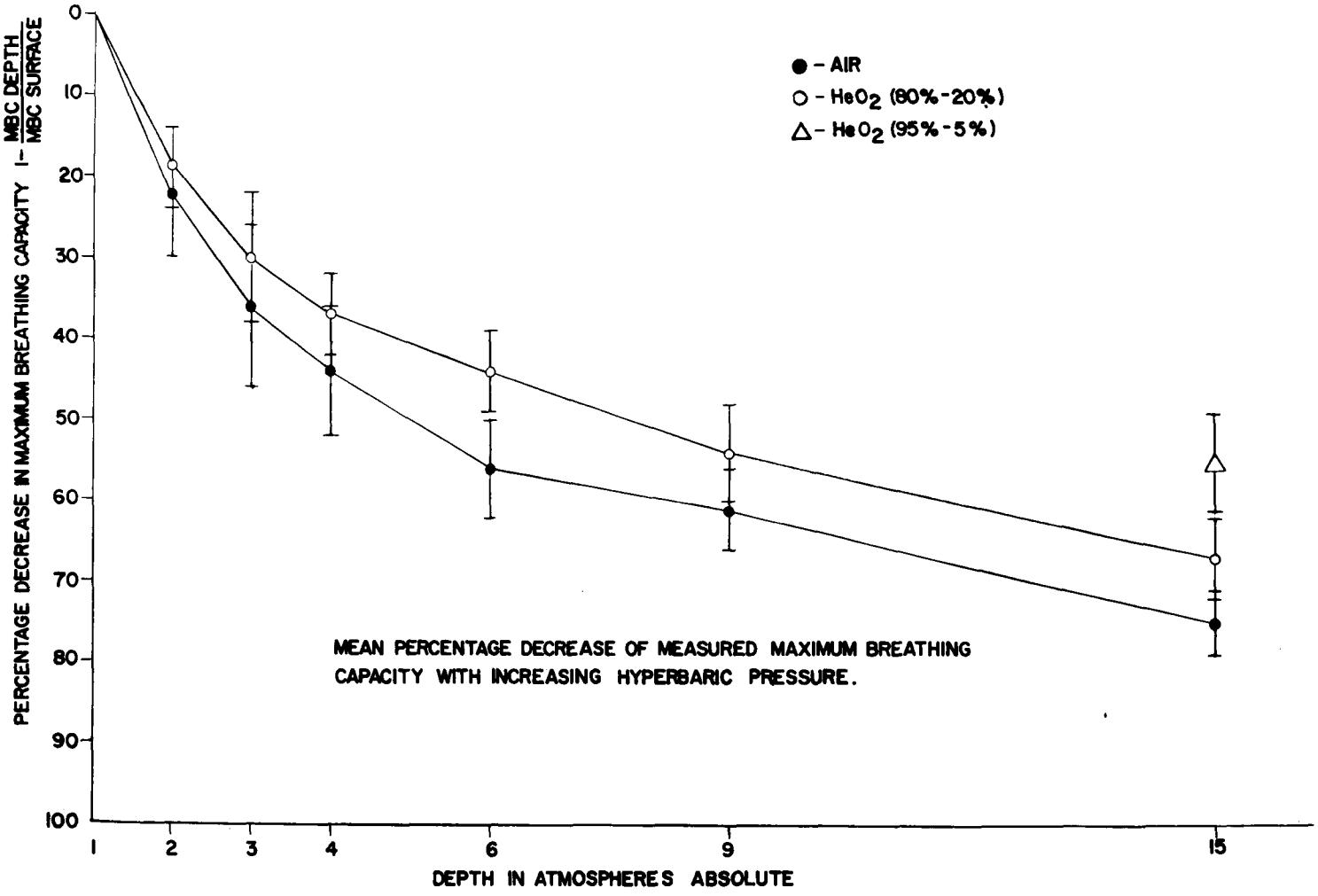
PERCENTAGE DECREASE IN MAXIMUM BREATHING CAPACITY 1- MBC DEPTH / MBC SURFACE
0
10
20
30
40
50
60
70
80
90
100
● - AIR
○ - HeO2 (80%-20%)
△ - HeO2 (95%-5%)
MEAN PERCENTAGE DECREASE OF MEASURED MAXIMUM BREATHING CAPACITY WITH INCREASING HYPERBARIC PRESSURE.
1
2
3
4
6
9
15
DEPTH IN ATMOSPHERES ABSOLUTE

Figure 2.

predicted normal, average value. At 15 atm there was a significant reduction in MBC with each gas mixture, however 77% of predicted normal remained with 95% helium.

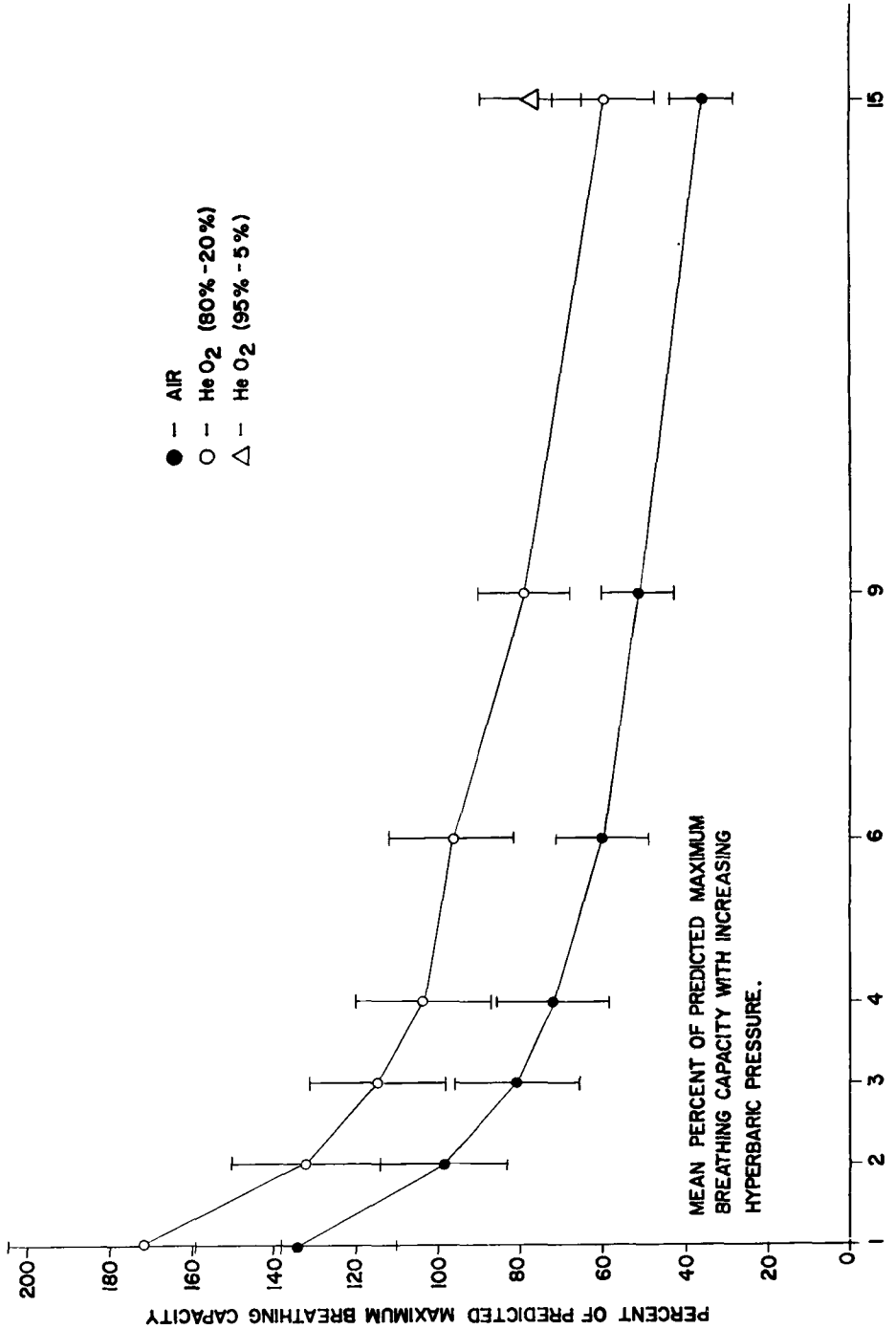

Figure 3.

There was a marked reduction in each segment of the timed vital capacity especially in the first and second interval, Figure 4. The upper half of the figure is the TVC for air, the lower half for helium-oxygen. With the subject breathing air a definitely obstructive impairment is produced. This effect is evident even in the moderate range of hyperbaric pressure (less than 7 atm). The three second timed vital capacity was less impaired, indicating a reduction in the peak expiratory flow.

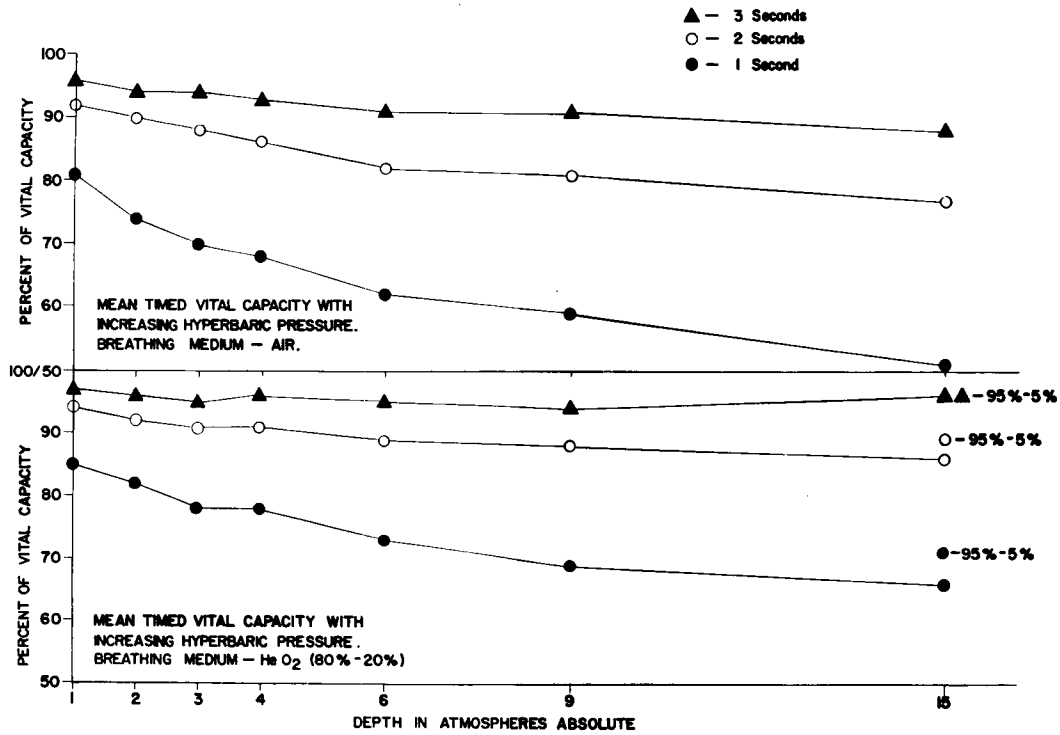

Figure 4.

The maximum sustained expiratory flow was calculated from the highest rate of volume flow sustained for 0.2 second and is expressed in liters per minute. The maximum expiratory flow showed rapid decrease with increasing density of the gases (Figure 5). However, the helium-oxygen mixture produced a more favorable result than a comparable nitrogen-oxygen mixture at all pressures tested. At 15 atm with 95% helium and 5% oxygen the flow rate remained near normal and was slightly more than twice that of air.

The mean percentage figures for each of the media are given in Tables III, IV and V.

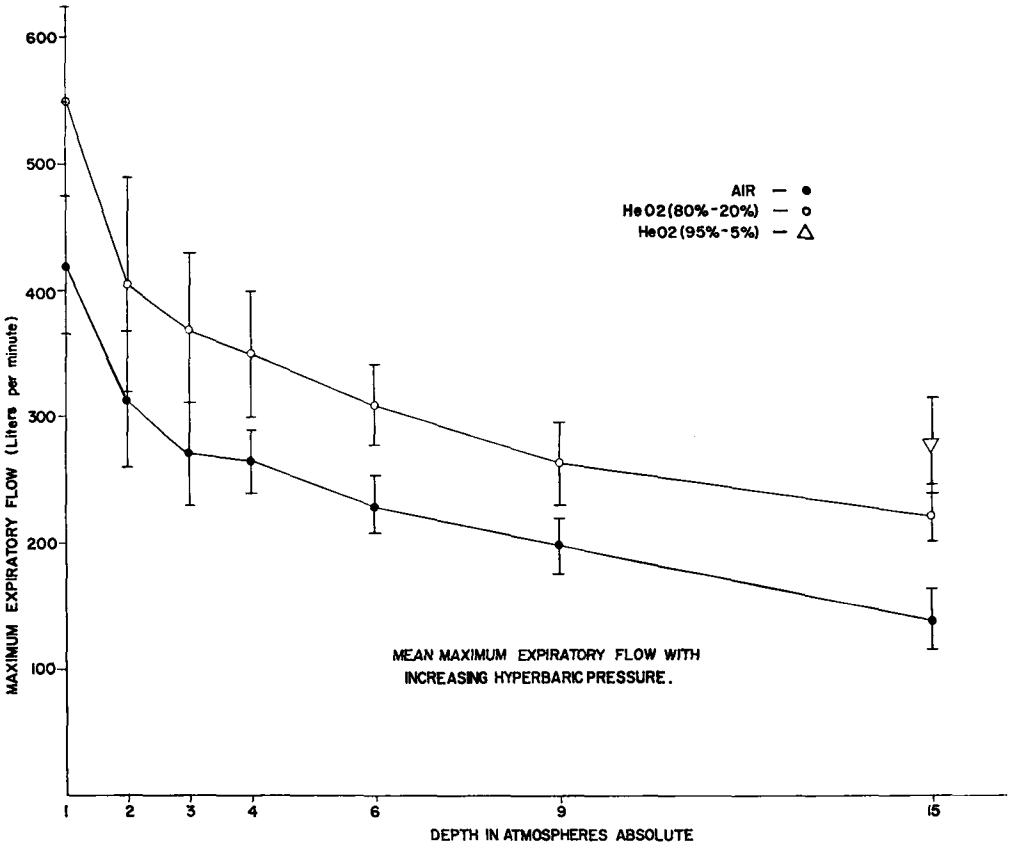

Figure 5.

DISCUSSION

The over-all effect of increased barometric pressure was a depression in all measured parameters of dynamic pulmonary function, with the development of an obstructive pattern. The most likely explanation for this finding is an increased non-elastic resistance secondary to increased density and is probably mediated through increased turbulence.

Workman has predicted a decrease in MBC proportional to increasing density using the formula $1/\sqrt{\text{Density}^{(4)}}$. The graphic presentation of this predicted decrement curve is given in Figure 6. His figures agree fairly closely with our experimental findings. The two would perhaps fall more closely together had the same base line been used as reference. Workman assumed the hypothetical man to have 100% of predicted MBC on air and an MBC greater than 100% of normal on He_2O_2. Our subjects were actually found to have a greater than 100% predicted MBC breathing both air and helium-oxygen mixtures. Workman also calculated a decrement curve with the subject breathing a 92% helium-8% oxygen mixture whereas our subject breathed an 80% helium-20% oxygen mixture and at 15 atmospheres also breathed 95% helium-5% oxygen.

TABLE III

Results of Measurements of Ventilatory Dynamics at Pressures of 1 to 15 Atmospheres Absolute Breathing Medium - Air*

Depth (Atm Abs)	Percentage Decrease in MBC		Percentage Predicted MBC		Timed Vital Capacity (%)						MEF (L/min)	
					1 sec		2 sec		3 sec			
	Mean	±SD	Mean	± SD	Mean	±SD	Mean	±SD	Mean	± SD	Mean	±SD
1	—	—	135.1	24.7	81.2	6.8	92.3	3.6	96.4	2.1	421	54.6
2	22.5	7.8	99.3	14.7	73.9	9.5	89.5	4.7	94.3	3.3	313	54.9
3	36.5	9.9	81.0	14.3	70.4	7.1	87.5	6.1	94.1	4.3	271	39.5
4	43.8	8.5	71.8	13.0	68.1	6.4	86.3	5.0	93.2	4.0	266	25.1
6	55.8	6.5	60.1	10.6	62.5	7.5	82.4	6.3	90.6	4.4	230	22.6
9	60.6	4.6	51.1	8.6	59.4	7.4	81.1	7.2	91.3	4.6	199	21.6
15#	75.4	4.0	34.8	7.5	50.9	6.5	77.3	8.1	88.5	6.5	140	23.0

*N = 11
#N = 8

TABLE IV

Results of Measurements of Ventilatory Dynamics at Pressures of 1 to 15 Atmospheres Absolute Breathing Medium - Helium Oxygen (80%-20%)*

Depth (Atm Abs)	Percentage Decrease in MBC		Percentage Predicted MBC		Timed Vital Capacity (%)						MEF (L/min)	
					1 sec		2 sec		3 sec			
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
1	–	–	171.5	32.9	85.0	5.8	93.7	3.4	97.0	2.2	548	76.8
2	18.8	5.3	132.2	18.0	81.6	6.2	92.3	4.2	95.9	3.0	407	84.2
3	29.5	5.7	114.8	17.4	77.9	7.1	90.8	3.5	95.3	2.5	370	60.0
4	36.6	4.9	103.5	16.8	78.2	7.2	91.4	4.8	96.0	2.6	351	48.7
6	44.2	5.2	95.8	15.3	73.3	9.1	88.6	5.8	94.6	3.7	310	32.4
9	53.6	5.9	78.8	10.7	68.8	7.0	87.5	5.1	93.9	3.5	264	34.3
15**	66.8	4.8	59.0	12.4	66.1	6.2	85.8	11.2	96.4	2.6	223	21.2

*N = 11
**N = 10

TABLE V

Results of Measurements of Ventilatory Dynamics at Pressure of 15 Atmospheres Absolute. Breathing Medium - Helium Oxygen (95%-5%)*

	Mean	± SD
Percentage decrease in MBC	54.4	6.0
Percent of predicted MBC	76.8	11.9
Timed vital capacity (%)		
1 second	70.9	8.2
2 seconds	89.7	3.5
3 seconds	96.3	2.6
Maximum expiratory flow (L/min)	281	38.4

*N = 9

Workman's calculations are very similar to Miles'[2] figures calculated utilizing respiratory gas of similar composition; however, Miles appears to have made an error in calculation at the lower pressures.

Mead[5] has shown that Reynold's number rather than Rohrer's equation more accurately predicts the true effect of changing density and viscosity on turbulence. The net effect on resistance would be proportional to the ratio of density to viscosity, or to the kinematic viscosity. Resistance would then be directly proportional to the density and inversely proportional to the viscosity. With an increased density there would be increased turbulence, however, with increased viscosity the turbulence would actually be decreased. The net effect then on resistance would be proportional to the ratio of density to viscosity, or to the kinematic viscosity.

Lanphier[6,7] observed a decreased respiratory minute volume (RMV) and elevation of the alveolar and blood Pco_2 in underwater swimmers. He made observations on several subjects with varying respiratory media including oxygen, air, helium-oxygen (55-45%) and nitrogen-oxygen (55-45%) at increasing atmospheric pressure to 5 atm (132 feet sea water equivalent). The decrease in RMV was greatest on air at 5 atmospheres but was decreased in proportion to the normal response expected for the observed alveolar Pco_2 in all instances. The exact etiology of this depression was unclear but depressive effects of nitrogen on the respiratory center and increased breathing resistance were suggested. It is unfortunate that mixtures of high oxygen content were selected for comparison since this produced a respiratory mixture of high density.

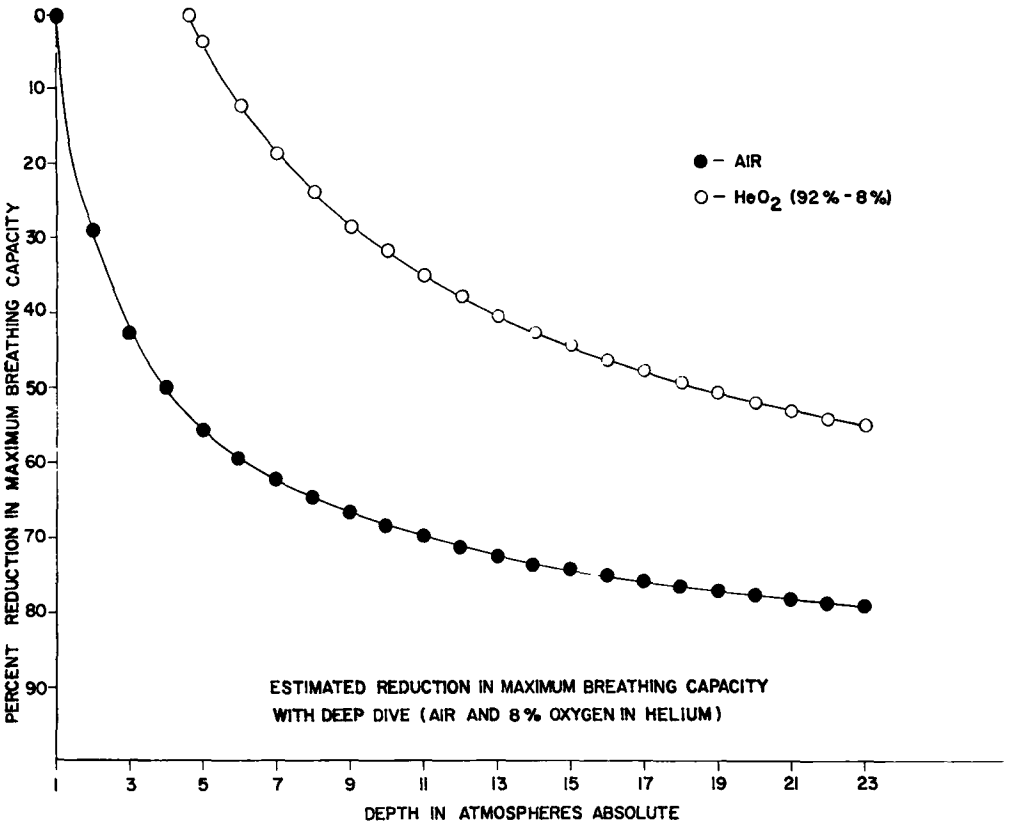

Figure 6.

Interpreted in the light of presently existing data, the finding of a decreased RMV in underwater swimmers breathing air or nitrogen-oxygen mixtures is not surprising. It is clear that the total work required for breathing is increased in terms of effort expended and oxygen consumed in performing respiratory work when breathing a gas of high density. If the efficiency of the respiratory muscles is comparable at hyperbaric states to that of the emphysematous patient, as is the alteration in the respiratory pattern, the oxygen requirement to move the same volume of air is greatly increased. Cherniak[8] has shown that in the emphysematous patient the oxygen cost of breathing may be as high as 19.5 ml per liter of ventilation, or nearly 16 times the normal mean, and that mean efficiency of a similar group was 1.8%. He attributes this difference to a greater work load. Other investigators have shown similar figures for oxygen costs of breathing with slightly lower respiratory muscle efficiency. There can be no doubt that the work required for breathing is greater with increased density of gases. Mead[9] attributes a part of this increased work requirement to inertia of the air with increased ambient pressure.

An apparent paradox exists, however. Even with the increased breathing resistance there appears to remain sufficient ventilatory capacity to meet the

physiologic needs for oxygen, at least for mild activity, yet the respiratory effort appears insufficient to produce adequate alveolar ventilation. As a consequence the alveolar Pco_2 is elevated to abnormal and even dangerously high levels. A comparable Pco_2 in the normal individual at 1 atmosphere would evoke a nearly maximum ventilatory response, near 75 to 100 L/min. In the underwater swimmer at increased barometric pressure however there is only a slight increase in the RMV. Several possible explanations exist. First, there may be an altered responsiveness to ventilatory stimuli due to the effect of increased barometric pressure per se. Secondly, the narcotic effect of the nitrogen may selectively depress the responsiveness of the respiratory center to arterial Pco_2. Lastly, factors not customarily considered of importance in respiratory regulation at 1 atmosphere may play a much greater role when the subject is exposed to hyperbaric pressure.

Zocche, Fritts and Cournand[10] have shown that only about 50% of the MBC is available for prolonged hyperventilation. If driven to the limit of capability the respiratory center responds by accepting a less than adequate alveolar ventilation in order to reduce the total work. Cherniack[11] and Eldridge[12] found a compromise between total work and accepted alveolar Pco_2 in normal subjects whose MBC had been decreased by artificial obstruction. Zechman[13] noted that graded airway resistance had a small effect on respiratory flow rate in subjects at rest but during periods of greater ventilatory demands a dramatic effect on total flow restriction and alveolar gas composition was observed. There was a rising alveolar Pco_2 even though the respiratory apparatus was potentially capable of greater ventilatory response. The common factor in ventilatory responsiveness in each of these studies and the studies on emphysematous patients is the oxygen cost of breathing[14,15].

Lanphier's subjects demonstrated a greater decrease in RMV than might have been expected from the added work of breathing alone. In all instances the oxygen partial pressure was from 100% to 200% of 1 atmosphere. High oxygen pressure has only a slight respiratory effect on the normal resting individual[16] but depression of respiration is observed in the emphysematous patient and is usually dependent upon the presence of either hypercapnia or hypoxia[17,18]. Bannister and Cunningham and Lloyd, Jukes and Cunningham found that high oxygen pressures during exercise decrease the RMV and produce a rise in alveolar Pco_2 in normal individuals[19,20,21,22].

When the work of breathing is increased, the presence of a normal or slightly decreased alveolar Po_2 may be of great importance. The removal of this stimulus by hyperoxia may play a very significant role in production of hypoventilation and hypercapnia. That this alteration in respiratory control does not require a prolonged period of adaptation but may be present within thirty minutes has been demonstrated by Barnett and Peters[23].

CONCLUSIONS

The capacity of the respiratory apparatus is markedly diminished by an increasing density of the respiratory gases.

The decreased ventilatory capacity of the human respiratory apparatus is probably the result of increased work of breathing produced by increased turbulence. Previously observed alterations in the RMV and hypercapnia in underwater swimmers can probably best be explained by the greater oxygen cost of breathing and the effect of hyperoxia on respiratory control, rather than by narcotic depression of the respiratory center by either nitrogen or carbon dioxide.

The significance of the decreased RMV and hypercapnia in the presence of hyperoxia as mediators of oxygen or carbon dioxide convulsions in underwater swimmers is not proven but seems very probable. The use of helium-oxygen mixtures rather than nitrogen-oxygen mixtures as the respiratory medium in specialized underwater breathing equipment seems highly desirable.

Further study should be done on the actual work of breathing, the respiratory response to O_2 and CO_2, and normal ventilation and Pco_2 measurements under conditions of grossly increased ambient pressure.

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INFLUENCE OF INCREASED AMBIENT PRESSURE UPON ALVEOLAR VENTILATION

E. H. Lanphier
Department of Physiology, School of Medicine
State University of New York at Buffalo

Under almost all circumstances underwater, the partial pressure of oxygen in the inspired gas is abundantly high. Concern about alveolar ventilation at depth thus generally relates to the adequacy of removal of carbon dioxide, hence the alveolar partial pressure and arterial tension of that gas.

Abnormal elevation of arterial Pco_2 can, of course, be undesirable in itself. We know that this normally produces respiratory stimulation and distress and that certain levels can produce a variety of other effects including impairment or loss of consciousness. There is also very good reason to believe that CO_2 excess can accelerate the onset of convulsive oxygen poisoning. In addition, it appears to potentiate the narcotic effects of inert gases and may well play a role in decompression sickness.

Other speakers have presented quantitative data concerning the effects of increased ambient pressure upon the respiratory capabilities of man, and it seems clear that under certain conditions of breathing medium and depth, a diver would be quite incapable of maintaining alveolar ventilation adequate to support a useful degree of physical exertion. The value of such information is obvious. However, there remains a very large range of depths in which adequate ventilation for useful exertion is at least theoretically possible but cannot be assumed to occur. The object of ultimate concern is the actual level of alveolar ventilation and arterial Pco_2 that a diver will spontaneously maintain under various conditions.

In my paper at the first Underwater Physiology Symposium[1], I described a specific problem in this area and our very early attempts to deal with it at the Experimental Diving Unit. In brief, we suspected that divers were not breathing adequately during exertion with nitrogen-oxygen mixtures at moderate depth and, because of resulting elevation of arterial Pco_2, were rendering themselves unusually susceptible to oxygen poisoning. During the three years following that meeting, we conducted extensive investigation of the problem. The findings were duly recorded in Experimental Diving Unit reports[2,3,4] but not otherwise published. Today, I wish to present some of the salient findings.

METHODS

The measurements to which I will refer were made in men swimming underwater against a known force (8 lbs) on the "swim-ergometer"[5] in a pressure tank at the Experimental Diving Unit. At this work rate, average oxygen uptake values were in the 1.2 to 1.4 L/min (STPD) range. We had developed methods of measuring expiratory minute volume, respiratory frequency, tidal volume, and external respiratory pressures under these conditions. The measurement of greatest interest was end-tidal Pco_2, obtained with a specially designed

pneumatically-operated continuous automatic sampling system. The breathing apparatus used in most of the experiments to be cited was a modified Scott Hydropak mask. Its demand unit was equipped with an extra tilt-valve, which operated the end-tidal sampling system. A mouthpiece arrangement within the mask reduced the dead space to a low value. In later experiments, the expired gas was led to a mixing chamber on the subject's back. Mixed expired gas was then sampled continuously by a device linked to the end-tidal sampling system. This permitted CO_2 output to be computed. Arterial blood sampling was ruled out not only by the difficulty of obtaining samples under the conditions of the experiments but by the fact that available man power did not permit us to set up then-available methods for accurate blood gas measurements.

RESULTS

I will concentrate upon presenting the end-tidal Pco_2 values that were obtained. With virtually no exceptions, the other measurements obtained simultaneously were consistent with the magnitude and direction of end-tidal changes and add little to the basic story. Figure 1 shows the main findings related to the basic question. The first bar indicates the mean end-tidal Pco_2 found in groups of 10 to 17 men swimming about four feet beneath the surface and breathing air. The mean value of 47 mm Hg is unusually high for such near-normal conditions, and many of the subjects showed higher values. (In all of these figures, the highest value obtained is indicated by the small line and cross-bar.) Here, the highest value was 53 mm Hg which is grossly abnormal for these conditions. Our first reaction was to doubt the validity of our end-tidal measurements, since it is possible for these to yield values above the mean arterial Pco_2 during exertion. However, later studies[3] showed a mean end-tidal-arterial Pco_2 difference of only 0.6 mm Hg in six subjects under similar conditions. In the man showing the highest arterial value, the end-tidal sampler yielded a value 4.2 mm Hg lower. The greatest "over-estimation" by end-tidal sampling was 2.7 mm Hg in the man who showed the lowest arterial value.

Although we lack comparable proof of the validity of our end-tidal Pco_2 values by actual comparison with arterial values under the other conditions of study, other lines of evidence also indicate that they are essentially reliable. At any rate, let us next consider the right-hand bar in Figure 1. This represents values obtained with at 55% N_2 - 45% O_2 mixture at 4 atm. (These were essentially the conditions under which we had encountered unexpected evidence of oxygen toxicity in earlier studies.) In one group of 17 subjects, the mean Pco_2 was 55 mm Hg. In a smaller group studied later, it was almost 52 mm Hg. In both instances, the "high man" exceeded 70 mm Hg.

Superficially, at least, such values seemed explanation enough for acceleration of the onset of oxygen poisoning. They also appeared to render impossible the approach to "mixed-gas SCUBA diving" with which we had hoped to overcome some of the problems of decompression[6]. We felt impelled to see whether we could determine the reason for the depression of respiration that caused such elevations of Pco_2. Only three likely possibilities occurred to us:

1) The work of breathing was obviously greater at depth than at the surface, and it was known that increased respiratory work could reduce the volume of ventilation especially during exertion. However, the breathing apparatus used had better breathing characteristics than most types of SCUBA, and there were no complaints even from "finicky" breathers like myself. At first glance, this did not seem a promising explanation.

2) The Oxygen partial pressure was considerably higher than at the surface, and oxygen had been reported to reduce respiratory drive during exertion. However, this factor had also been present during the oxygen tolerance studies[7] whose results were contradicted by findings with gas mixtures.

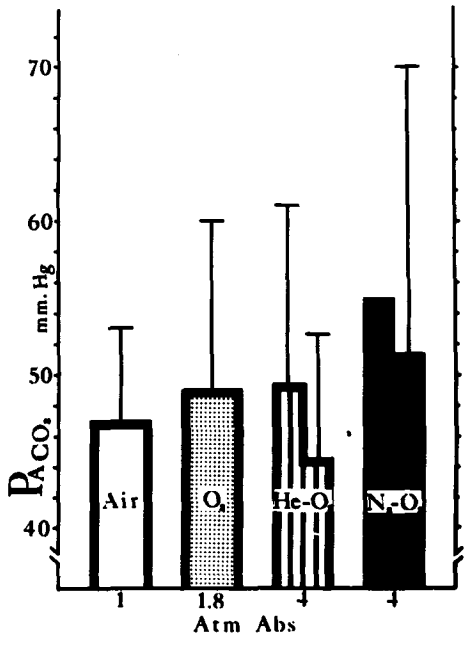

Figure 1. Effect of Ambient Pressure and Breathing Medium upon End-tidal Pco_2 during Working Dives

3) The partial pressure of nitrogen was also higher at depth. It was not high enough to produce any awareness of nitrogen narcosis, but we wondered if it could not have some depressant effect upon the respiratory center even in this range.

At any rate, we then began to manipulate the variables in the hope of discovering the explanation for the great elevation of Pco_2.

Of greatest practical importance was the finding that the exceptional elevation seen at 4 atm was largely eliminated by substituting helium for nitrogen in the mixture. Alveolar ventilation was higher, CO_2 production was about 10% lower (possibly reflecting decreased work of breathing) and the end-tidal Pco_2 was only about 2 mm Hg above the surface-air value, as can be seen in Figure 1. In one group, which included fewer "high CO_2" men, the value was even lower than at normal pressure, indicated by the right hand portion of the He-O_2 bar. Here the Po_2 of the breathing medium was the same, but the density was about half that of the N_2-O_2 mixture, and nitrogen was absent. Breathing pure oxygen at 26 feet of the depth (1.8 atm) gave the same Po_2, about the same density, and very nearly the same resultant end-tidal Pco_2 and He-O_2 at depth: in both cases, about 2 mm Hg above the surface value. Thus, a moderate increase in density plus high Po_2 did not seem to explain more than about one-quarter of the total elevation of Pco_2 seen with the N_2-O_2 mixture at depth.

It was obvious at this point that He-O_2 mixtures would be far more desirable for "mixed gas diving" than N_2-O_2 mixtures, but we remained interested in the reason for high Pco_2 values seen with the latter. I should emphasize that

large changes and very high values were seen only during exertion, and very little elevation of P_{CO_2} was found in resting exposures. For that reason, I was not surprised when Dr. Hesser's very ingenious and careful studies of respiratory control at rest at depth failed to show any changes attributable to narcosis[8,9]. During exertion, all of our subjects showed the kind of changes described; but the men who had high end-tidal P_{CO_2} even at normal pressure were the ones who showed really impressive elevations.

ROLES OF P_{O_2} AND P_{N_2}

Figure 2 sheds a little more light on the roles of oxygen and nitrogen pressures. The effects of three different nitrogen-oxygen pressures were compared at 4 atm: 1) about 5% oxygen in nitrogen, 2) air and 3) the 45% oxygen mixture. These provided a range of inspiratory oxygen partial pressures from about 0.2 atm (as with air at normal pressure) to 1.8 atm but at the same time a range of nitrogen pressures from about 3.8 atm down to 2.2 atm. The densities were approximately the same. If nitrogen had any depressant effects, these were apparently overshadowed by those of oxygen, since the P_{CO_2} increased with increasing oxygen pressure. The mean difference between the extremes was only 2 mm Hg, about the same as that attributable to increased oxygen pressure and a small increase in gas density in the previous comparison. (As in many of the comparisons I shall cite, most of the subjects showed similar changes; but the range of individual values was such that the mean differences were not statistically significant.)

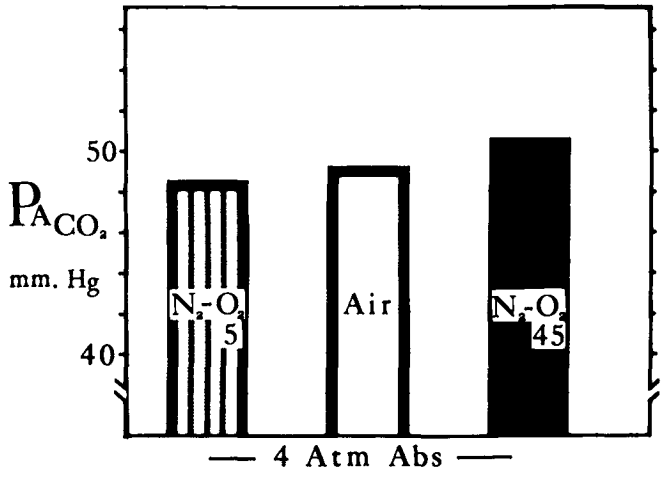

Figure 2. Influence of O_2 Concentration of N_2-O_2 Mixtures upon End-tidal P_{CO_2} of Working Divers at 4 atm abs

ROLE OF RESPIRATORY WORK

In a small study conducted at the Experimental Diving Unit, Marshall and DuBois and I[10] had shown that the work of moving air through a diver's own airways was approximately doubled in going from normal pressure to 4 atm but that it was approximately normal with a helium-oxygen (80%-20%) mixture at that pressure. The work of moving air through the breathing apparatus also increased at depth. Although it was impossible for us to modify the "internal" work of breathing with a given gas mixture at a given pressure, we were able to increase or decrease the respiratory resistance of the external breathing circuit to some extent. Figure 3 shows the effect upon end-tidal P_{CO_2} of such manipulations. The two bars labeled "normal"

indicate values obtained with our usual breathing apparatus with air and a He-O_2 mixture (55%-45%) respectively. We lowered the external work with air by using a special apparatus having no less than five demand valves, and the mean end-tidal Pco_2 was 1 mm Hg lower. When we artificially increased the external work of breathing with the He-O_2 mixture, it went up 3 mm Hg. Our intent in this case had been to simulate the total work of breathing with air, but layer analysis indicated that we had not quite matched the external work with air, much less simulating the added internal work of breathing with the denser gas. About all we can say is that changes in airway resistance appear to produce changes in the right direction in alveolar ventilation and end-tidal Pco_2. If we had increased the work with He-O_2 sufficiently we might have been able to show that all or most of the increase in end-tidal Pco_2 at issue was caused by increased work of breathing. As it was, the possible role of narcosis in depressing respiration continued to interest us.

EFFECTS OF ADDED DEAD SPACE

In the study that had raised the question of increased susceptibility to oxygen poisoning, an ordinary Scott Hydropack mask without integral mouthpiece had been used. We were well aware that this added external respiratory dead space, but it required a considerable research effort to be sure how much of the internal volume of the mask was actually "dead"(5a). When we finally obtained a value of 500 ml we tried adding this much dead space to the experimental circuit while measuring end-tidal Pco_2. The results are shown in Figure 4. The mean Pco_2, already rather high with air at 4 atm increased another 6 mm Hg. This suggests that some of the Pco_2 values during the original study may have been very high indeed. It seems likely that a man who already had a marked tendency to retain CO_2 would be even more adversely affected by added dead space than others. However, we did not find a disproportionate rise in the "high man" value here.

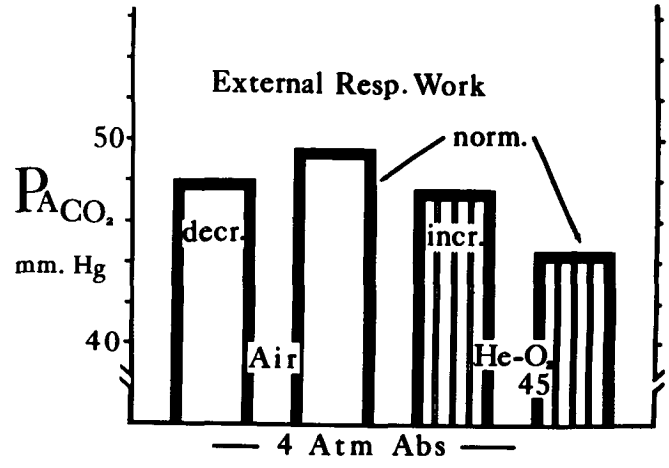

Figure 3. Effect of Alteration in External Work of Breathing upon Mean End-Tidal Pco_2 of Working Divers at 4 atm abs

EFFECTS OF EXERTION, PER SE

The findings of greatest general physiological interest were obtained in Dr. Lambertsen's laboratory when we took five of the "high CO_2" divers to Philadelphia for special studies, including arterial Pco_2 determinations. The crucial discovery is indicated in Figure 5. Here it is evident that these men showed a very large and abnormal increase in end-tidal and arterial Pco_2 simply in the

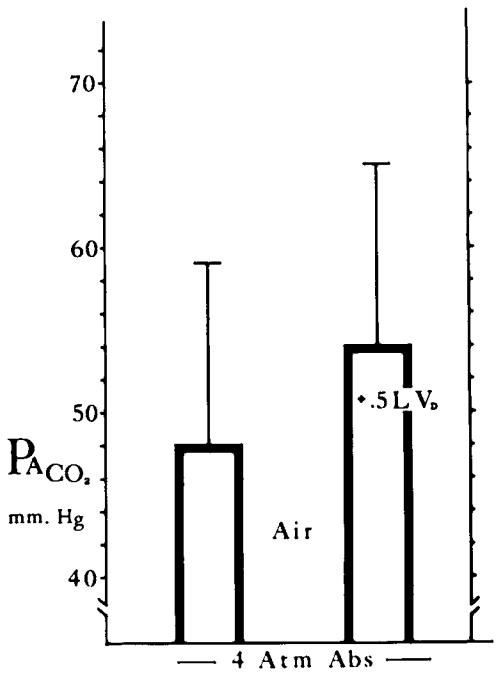

Figure 4. Change in End-tidal Pco_2 with added Respiratory Dead Space in Working Divers Breathing Air at 4 atm abs

process of going from rest to moderate exertion. These measurements were made a normal pressure on dry land, breathing air. One man reached almost 57 mm Hg. This was the same man who had experienced an oxygen convulsion in 20 min during work when breathing a nitrogen-oxygen mixture at depth, at an oxygen exposure equivalent to pure oxygen at only 29 feet of depth. Whether the breathing apparatus had high resistance or negligible resistance made little difference in the rise of Pco_2 associated with exertion in these men. Most of them showed markedly subnormal respiratory responses to inspired CO_2 as well. They seemed to represent a breed apart from the normal run of men, and we still are not sure why. That these differences represent adaptive changes to diving is the most interesting hypothesis. The picture closely resembled that reported by Schaefer in submarine escape training tank instructors, but we lacked the longitudinal studies which indicate an adaptive change in that instance, and we are not sure what factor in the type of diving that these men had done could account for such a change.

The finding that certain divers showed a marked increase in arterial Pco_2 during exertion has led Lambertsen and his associates[11] to speculate about the effect of exertion in accelerating the onset of oxygen convulsions. Since most of the observations leading to that conclusion had been made in experienced divers, it appears possible that a tendency to retain CO_2 in exertion explained the finding. Exertion might not necessarily decrease oxygen tolerance in a man who did not retain CO_2, or under circumstances where a rise in arterial Pco_2 was prevented.

RECENT STUDIES

More recent work supported by the Office of Naval Research in our laboratory at Buffalo has not primarily concerned the regulation of alveolar ventilation during exertion, but some of our findings apply to the same general problem. For example, we have found no evidence of significant elevation of alveolar or arterial Pco_2 in resting exposures to air at pressures to 7.8 atm abs. Almost invariably the subjects have clearly been affected by nitrogen narcosis, so the normality of their Pco_2 values suggests not only that narcosis does not depress respiration at rest but also that narcosis does not depend upon elevation of arterial Pco_2[12].

Our experiments during exertion have all involved work rates at which limitations of the breathing apparatus and of the subjects' own airways have prevented adequate alveolar ventilation and produced very marked dyspnea. For this reason, they shed little light on the P_{CO_2} values a diver might choose to maintain under less rigorous conditions.

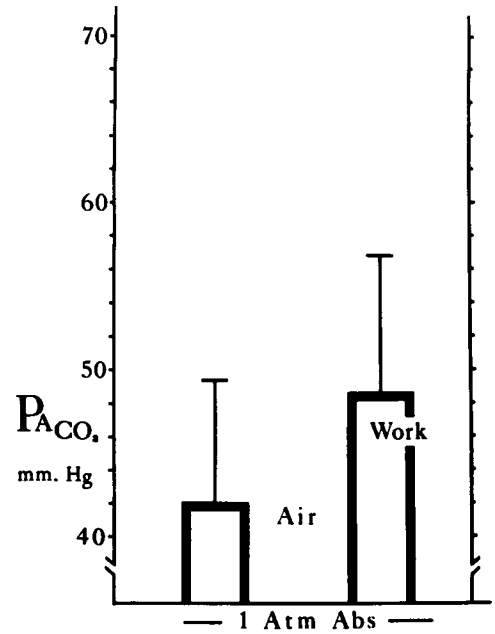

Figure 5. Alteration of Arterial P_{CO_2} by Exertion with Air at Normal Pressure in CO_2-retaining Divers

We are not reasonably certain that, as Case and Haldane tried to tell us in 1941[13], elevation of P_{CO_2}, when it occurs at depth, greatly enhances the narcotic effects of inert gases. With air at 7.8 atm exertion with restriction of breathing produces a marked rise in P_{CO_2}, and the subject can go from definite but mild narcosis to coma within about three minutes. We are interested in the effects of nitrogen, and nitrogen plus exceptionally high P_{CO_2}, upon the respiratory drive associated with exertion. To date, however, we know only that severe impairment of consciousness is not accompanied by abolition of the respiratory drive. Loss of consciousness naturally obliterates awareness of dyspnea, but an appalling sense of distress returns before the mind clears up enough to identify the distress as dyspnea or to think conforting thoughts about its transitory nature. The result is a period of terror that has no equal in my experience.

CONCLUSIONS

Experimental Diving Unit studies that I have cited indicate that inadequate alveolar ventilation and CO_2 retention can arise and cause serious problems under conditions that are not all rigorous by most standards. Some of the best divers are for some reason the most prone to such problems, showing considerable retention of CO_2 during exertion even under normal conditions. Increases in P_{O_2} or density of the breathing medium appear to produce some degree of retention in all working divers, with especially marked changes in the individuals mentioned. Increased respiratory work in the breathing apparatus or added external dead space can produce further elevations of arterial P_{CO_2} at depth.

Under the conditions investigated, most of the problems could apparently be circumvented by using helium-oxygen mixtures and better breathing apparatus. However, we are now moving into another range of depths and pressures where we can be almost sure that similar problems will arise even with the best gas mixtures and breathing systems. Breathing appliances that will actively assist the diver's respiratory efforts obviously deserve development and study, but there

is reason to believe that there are definite limits to this approach. Personnel selection procedures may be worthwhile but can scarcely provide a full solution to the problem.

Since most of the difficulties arise as a result of the metabolic demands of physical exertion, we must clearly spare the deep diver from all unnecessary work by providing propulsive devices and all other practical aids. However, a diver who cannot exert himself at least to a moderate degree becomes scarcely more useful than a TV camera with a remotely-controlled manipulator. It seems important in the very near future to find out at what depth and duration of dive the human must logically give way to the machine. It seems quite possible that some of our present ambitions for diving already extend beyond that point.

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THIRD SESSION
RESPIRATORY EFFECTS OF INCREASED PRESSURE

H. Rahn, Chairman

INTRODUCTION

For our final session today we will change our focus from the whole man to the lung. Exactly 80 years ago an extremely interesting experiment was carried out underwater. It was not intended to shed any light upon the problem of deep sea diving, but in spite of this fact its aqueous origins were quite prophetic of some problems which exist in pulmonary ventilation under pressure. I will quote the exact words of the author as he described his experiments. He said, "In 1883 I succeeded in proving by means of experiments with colored water jets that, when water is caused by pressure to flow through a uniform, smooth pipe, the motion of water is viscous or sinuous (meaning turbulent), according as the mean velocity of the water is below or above a critical value." By now you will have recognized the words of Osborne Reynolds and that the certain value which he described in this paper changes the stream from a viscous flow to a turbulent flow.

$$\Delta P = k_1 \dot{V} + k_2 \dot{V}^2$$

turbulence occurs when

$$\dot{V} \left[\frac{2 \text{ density}}{\pi r \text{ viscosity}} \right] = \text{Reynolds}$$

$$\dot{V} \times \text{density} \times k_3 = 2000$$

The volume flow times the density divided by the viscosity is equal to R or the Reynolds number. Now if we expose a man to a gas pressure, the viscosity of the gas is not apt to be changed, the geometry is not changed and so we have the lower expression in the figure. This states that when the volume flow times the density times a constant, which is dependent upon the geometry and the viscosity, is equal to 2000, then the flow changes from viscous to turbulent. We cannot substitute pressure for density and the equation states that if we double the pressure, the volume flow will be halved and the stream changes from viscous to turbulent. The top equation simply is an expression of the mechanical pressure in the respiratory system which is required to move gas.

The first part of that equation, k_1, is simply Poiseuille's Law. This is unaffected by the changes in density on compression. The second part is the additional pressure which is needed to overcome the resistance which occurs due to the turbulence of air streams. This is proportional to k_2 times the square of the volume flow. As we now raise the ambient pressure of the man, k_1 will presumably remain the same but k_2, the turbulence factor, will vary. With this general introduction we may begin the session on pulmonary ventilation.

DISCUSSION

RAHN: I am impressed that if measurements of ventilation are to be made under high pressure it will be necessary to be particularly careful about the instruments which are used. Apparently they can have a profound influence upon "normal" ventilation even at sea level.

WOOD: We were aware of this problem in our own studies. Certainly the resistance offered by the Collin's respirometer is high when you get into measurements of maximal breathing capacity. However, it is not greater than that of most open-circuit SCUBA apparatus. Therefore, I think the values we have obtained are applicable to the use of underwater breathing apparatus and SCUBA diving. They may not be entirely applicable to pure physiological situations.

LANPHIER: Dr. Wood will take comfort from a slide that I have. Captain Mayo of the Air Force has been working in our laboratory on this problem of ventilation at increased pressure. We have superimposed on Dr. Wood's data the values which Captain Mayo obtained using a wedge spirometer, which has some theoretical advantages. We see an almost astonishing agreement between most of the points. We differ at one atmosphere where we have considerably higher values. This may reflect differences in the apparatus or the subjects. Another point that intrigues me very much is the fact that we got definitely lower values on helium at 7.5 atmospheres. Our chamber will only go to 7.8 atmospheres, so we stopped here instead of going on to the 15 Dr. Wood reached. The agreement is reassuring. However, it indicates that if percent decrease is used as a means of expressing data, much depends on the values obtained in control studies at the surface. Captain Mayo also did the same experiments at one-half atmosphere (18,000 feet) and found an increase in maximal breathing capacity.

WOOD: Work of breathing at increased ambient pressure must be considered. We have searched for data concerning the work of breathing and pressure volume loops in exercise but have found very little which bears upon the problem at increased pressure. With the normal slow inhalation and slow exhalation of rest, a pressure volume loop is described which does not cross back over to the positive pressure side during exhalation. However, in exercise by a subject in a pressure chamber, exhalation is accomplished by positive intrathoracic pressure. This seems to be partly dependent upon the type of apparatus that is used. With positive pressure exhalation the work of breathing is greatly increased; this is perhaps even more significant than what we have already talked about.

RAHN: I will ask a very practical question. It would seem from Dr. Buhlmann's analysis and the speculations of others, that when we impose high work loads it is going to be almost impossible to maintain normal alveolar P_{CO_2} values. The practical problem is to measure how much P_{CO_2} rises. If we go to a depth of 500 feet and exercise at even a slight workload, we will, according to the analysis of Dr. Buhlmann, begin to increase alveolar P_{CO_2}. How shall we measure this particular end-result of increased resistance? If we now impose on top of this any type of flap valve system, we are going to further increase respiratory resistance. Certainly we will not obtain normal values for

alveolar gas. This then suggests that the only possible way of getting the effect of the added resistance is by measurements of arterial Pco_2. Is there any other way to approach this particular problem?

LANPHIER: I have nothing further to offer but I would agree that the problem of ventilation measuring apparatus that does not considerably increase the work of breathing at high ambient pressures is a very difficult one to solve. The arterial Pco_2 would give you the net effect. I don't think you would be able to measure the respiratory volumes at the same time very expeditiously.

RAHN: You can measure the respiratory volumes but I would feel these do not answer the question that we set out to ask.

WOOD: In some individuals at increased pressure the curve of times, forced exhalation comes down very sharply, then breaks and follows a less steep line. This is fairly typical of an obstructive pattern. Our pressure-volume analysis suggests that the obstruction is internal, that it is in the small bronchioles. If this is true, and if a great deal of resistance is in the major airways, then why should these small airways tend to collapse under these conditions?

DUBOIS: By "obstruction" we do not mean that the lumen of a bronchus is abnormally impaired by obstructive material, but rather that it collapses under the influence of high velocity with an increase of density. That would be because there is a greater pressure gradient between the alveolus and the bronchus. Therefore the pleural pressure acting on the outside of the bronchus tends to collapse it. This happens also in other instances in which there is a high pressure gradient from the alveolus along the axis of the airstream in the bronchus. I see no reason why it should not also happen with the increased gas density and with the elevated Reynold's number. The greater the drag in the air, the greater the resistance. Therefore it would then mimic asthma without being asthma.

WOOD: We observe this in only a few subjects. Are there people who have abnormal elastic properties in their lungs, which normally are not manifest, but which may suggest beginning abnormality?

RAHN: You are suggesting that a screening procedure or a new pulmonary function test is possible.

LANPHIER: I don't believe we have to presume any abnormality to agree with what Dr. DuBois has just suggested. Our lower values for maximum breathing capacities at 7.5 atmospheres in a helium-oxygen atmosphere suggested that a little more external resistance might have been beneficial. This sounds ridiculous at first but it might be worth investigating.

MACKAY (S): This question of measuring the breathing resistance at great depths is essentially to get at the pressure in the lungs. Why don't we build a very tiny pressure telemetering transmitter that we can hang on a very fine thread? You probably couldn't get it all the way down to the alveoli but I am sure you can go almost all the way. Obviously a piece of thread won't change the resistance to flow.

REHMAN: Placing foreign bodies in the respiratory tree requires consideration of the effects of stimulating the epithelial lining, which in turn might cause construction of the peripheral bronchial tree. On the other hand, it is now possible to place transducers in the esophagus or in the pleural cavity and measure changes in intrathoracic or intrapleural pressure.

The effects of the changes in pressure on the respiratory tree must themselves be considered, particularly when the Hering-Breuer reflexes modify the respiratory rate and the tone of the peripheral bronchial tree. Therefore the resistance cannot be considered only in terms of viscosity or rate of flow, but I think we also have to consider the physiological characteristics of the bronchial tree itself. Also, is it considered in calculating resistance whether we have laminar or turbulent flow in the peripheral bronchial tree?

BUHLMANN: It is not only the trachea, it is the whole bronchial tree.

HESSER: When dealing with carbon dioxide pressure, one must make arterial measurements directly. In a recent investigation, Dr. Martel has shown, by following directly the arterial Pco_2 and the end-tidal Pco_2, that the normal gradient is reversed during exercise. The end-tidal Pco_2 will be about 5 or 6 mm higher than the arterial at a work level of 600 Kg/min. I think this gradient might become still higher when working under high pressure because of the fact that the respiratory rate is decreased and the Pco_2 will increase even more. Therefore the end-tidal Pco_2 will become much higher than the mean arterial Pco_2.

RAHN: Thank you Dr. Hesser, this is a very important point because obviously it is easier to take an alveolar gas sample than an arterial one. You must also do the arterial gas analysis under high pressure.

BEHNKE: I don't know what is being measured in the studies described here. Is it the resistance in poor apparatus or the resistance in the lungs? The two have not been separated at all. Divers in helmets have not had the difficulties enumerated. Sampling from the arteries and doing all of these fancy things under pressure might be avoided; you might analyze the pH of the urine and do as Louis Shaw did, the curves of CO_2 uptake and CO_2 elimination after the run is over to determine the build up. Then there is another question relative to the difference between the SCUBA diver and the man in the chamber, insofar as the column of water may influence respiration? The last point is: Have you used apparatus that mechanically delivers the ventilatory volumes required to keep the CO_2 normal and then measure the forces?

RAHN: I think that an arterial Pco_2 measurement in a high pressure chamber, when there is no breathing apparatus encumbering the individual, is a very important measurement to make in order to answer this whole question. Dr. Buhlmann, do you have any comments to make upon Dr. Behnke's questions?

BUHLMANN: Our recording was made only in the dry chamber. Water is an additional resistance and it is necessary to move the water with the chest.

BEHNKE: There is an increased inspiratory resistance resulting from the

hydrostatic pressure. Pushing the air out isn't too much of a problem for healthy men.

LANPHIER: It depends entirely upon the design of the breathing apparatus. If the breathing apparatus is not designed properly you can have either inspiration or expiration assisted. It would be possible to design an apparatus, I am sure, in which a small valve changing its position would permit the hydrostatic pressure to assist in both phases of respiration. In our own underwater studies we had to do the best we could with the location of the demand valve and the exhaust valve, to eliminate as much as possible the hydrostatic effects on the work of breathing.

MACKAY (S): Would a negatively loaded transducer applied externally be of aid in measuring the air velocity?

LANPHIER: It would be extremely helpful if you could in any way measure the air flow reliably without adding to the respiratory resistance. This is obvious. We haven't been aware of anything that quite met this criterion as yet.

WOOD: The possibility of the measurement of volume change by chest wall impedance is now being used and may have promise.

DUBOIS: Was the increased alveolar CO_2 due to a decrease in alveolar ventilation or was it due to an increase in CO_2 production in the body under pressure?

LANPHIER: In going from helium-oxygen at four atmospheres to nitrogen-oxygen there was approximately a 10% increase in CO_2 production. When we apply the alveolar ventilation equation to this situation, we have to assume a larger dead space than we think existed to get our calculations to yield exactly the end-tidal CO_2 tensions. We feel quite sure, as Dr. Hesser pointed out, that there is an error of this kind.

CHEMICAL MECHANISMS IN OXYGEN TOXICITY

J.J. Thomas, Jr.
Lieutenant, Medical Corps, U.S. Navy
E.M. Neptune, Jr.
Commander, Medical Corps, U.S. Navy
Naval Medical Research Institute
National Naval Medical Center
Bethesda, Maryland

Since this meeting is concerned largely with the phenomena that occur at greater than atmospheric pressure, I shall be primarily concerned with the effects of high oxygen pressures on brain metabolism. We are particularly interested in biochemical alterations that could result in the rapid occurrence of violent excitatory phenomena such a myoclonus and grand mal seizures.

I should remark at the outset that an adequate comprehension of the relationships between metabolism and function in the nervous system is still only a distant goal, despite the great forward strides that neurochemistry has made in the past decade. This dilemma is particularly notable with regard to convulsive conditions, where it is not possible to indict a single specific biochemical "lesion" as the common cause of seizure activity[1]. No consistent relationship has been found between the initiation of seizures and the metabolism of acetylcholine, ammonia, glutamic acid or γ-aminobutyric acid, among others. However, interference with energy metabolism may initiate seizures, as is attested by the convulsive effects of hypoglycemia, hypoxia, thiamine deficiency and cyanide poisoning.

Haugaard presented an excellent and succinct review of the subject from the biochemical point of view at the last Underwater Physiology Symposium in 1955[2]. I shall summarize the salient features of that presentation, which are, in general, valid today:

1) Brain tissue is by far the most susceptible to the toxic effects of oxygen at high pressure[3,4,5].

2) A general depression of oxidative metabolism is not the direct cause of oxygen toxicity in the animal[6].

3) Some enzymes were poisoned, though slowly, by oxygen at from 2.9 to 8 atm (absolute). Most of the affected enzymes were dependent on sulphydryl or -SH groups for normal activity[5,7,8,9].

4) The time necessary for depression of respiration of brain slices in vitro was much longer than that required to produce severe neurotoxic symptoms in vivo, at equivalent pressures. This is quite apparent from Table I[10]. Homogenate preparations were affected by oxygen rather more rapidly, but the latent periods still did not correlate well, rate-wise, with the phenomena in vivo.

Furthermore, when neurochemical abnormalities did occur, they usually were irreversible, unlike the acute neurologic phenomena, in vivo.

TABLE I

Time Course of Poisoning of Brain Tissue Respiration by High Pressure Oxygen
From Dickens, F. (10)

Oxygen Pressure (Atm)	Average Time for 50% Poisoning (min)	Observer
2.9	180	Dickens
(3.0)	(105*)	Van Goor and Jongbloed
3.38	150	Dickens
4.4	100	Dickens
5.08	80	Dickens
8.0	75	Stadie, Riggs and Haugaard

Observations are for slices of rat brain cortex except* which were of chopped (rat?) brain tissue.

5) Haugaard concluded that the problem of acute oxygen toxicity would eventually resolve to effects of molecular oxygen on a few particularly sensitive and critical enzyme systems. Hypothetically this could occur by a reversible oxidation of essential cofactors containing sulfhydryl groups, rather than by direct inactivation of the enzymes themselves, which likely would be irreversible.

In short, the challenging problem for the biochemist is to find a critical site or sites in brain metabolism which is rapidly and reversibly affected by oxygen at high pressure, in contrast to the slow and irreversible inhibitions previously observed[3,4,5,7,8,9]. However, in all of those excellent and painstaking studies of brain metabolism at high oxygen pressure, the primary parameter that was measured was respiration, or total consumption of oxygen. More recent work with ^{14}C-labelled substrates has shown that less than one half of the oxygen consumption by brain (in vivo or in vitro) is directly related to the oxidation of glucose[11,12,13,14,15,16,17,18,19]. Thus it is quite conceivable that rapid alterations in the metabolism of brain slices have occurred during incubations at high oxygen pressure but were not detected by measurements of O_2 consumption. For this reason we decided to "reopen the case" and reinvestigate

basic carbohydrate metabolism in brain at high oxygen pressure by using more specific techniques. In particular we have concentrated on the production of ^{14}C-labelled carbon dioxide from ^{14}C-labelled glucose. For simplicity, we have used either homogenates or mitochondria prepared from whole rat brain. These tissue preparations were "fortified" by the addition of DPN^+, ATP, hexokinase, KCl and magnesium to stimulate maximal glucose metabolism. Most of our experiments were performed with oxygen at 0.2, 1.0, or 5.0 atm pressure (absolute) and lasted 30 minutes or less. Details of the procedure may be found in our publication[20] on this work.

Large increases in lactate production by this system were observed with oxygen at 5 atm pressure, which resembled the effects of anaerobiosis. This is quite apparent in Table II. Such effects at high oxygen pressure were accompanied by a marked increase in the concentration of pyruvate and a slight decrease in the utilization of glucose. Increased lactate formation could be observed within ten minutes of incubation at 5 atm Po_2. The increased production of lactate seems to agree with the increased concentrations of lactate in the venous blood of dogs breathing O_2 at about 5 atm reported in 1932 by Bean and Haldi[21].

TABLE II

Effects of High Oxygen Pressure on the Production of Lactate by Cell-free Preparations of Rat Brain Homogenate during 30 minute Incubations at 37°C

Gas Phase	Lactate Production (μmoles)
Air at 1 atm	5.7
N_2 at 1 atm	10.3
O_2 at 5 atm	12.3

Results are the means of closely agreeing triplicates.

We next studied the effects of oxygen at 5 atm on the production of $^{14}CO_2$ from uniformly ^{14}C-labelled glucose ([U-^{14}C] glucose). The greatly decreased production of $^{14}CO_2$ at 5 atm Po_2 is exemplified in Table III. Incubations for 20, 30 or 40 minutes in oxygen at 5 atm all resulted in decreases in the production of $^{14}CO_2$ to 20-35% of controls in oxygen at atmospheric pressure. Measurements of total CO_2 production, valuable despite their lack of much precision, have failed to disclose significant differences between the effects of oxygen at 1 and at 5 atm. Incubations with air at 5 atm did not result in decreases in the production of $^{14}CO_2$ as compared with oxygen at 1 atm. Addition of the cofactors coenzyme A (CoA) and thiamine pyrophosphate (TPP) did not alter the inhibition by hyperbaric oxygen, nor did high concentrations of catalase or reduced

glutathione (GSH). However, some of our latest results indicate that simulation of the glutathione reductase system, through the activation of the hexose monophosphate shunt (by the addition of TPN[16]), does exert a partially "protective" effect against oxygen at high pressure. This clue is being explored further, using [1-^{14}C] glucose, but at present it does not appear that the hexose monophosphate shunt is directly concerned with the effect of oxygen at high pressure on [U-^{14}C] glucose catabolism.

TABLE III

Oxidation of [U-^{14}C] Glucose

Po_2 (atm)	Counts/min in $^{14}CO_2$ Produced	Minimal Calculated μmoles of CO_2 Produced	Per Cent Control $^{14}CO_2$	Total μmoles of CO_2 Collected
1	161 ± 50(4)	1.94 ± 0.06	100	12.5 ± 2.5(4)
5	405 ± 29(4)	0.49 ± 0.03	25	10.5 ± 1.8(4)

20 μmoles of glucose uniformly labelled with ^{14}C and containing 100,000 counts/min were incubated with cell-free rat brain homogenate for 30 minutes at 37° C.

Since lactic acid and pyruvic acid concentrations are rapidly increased at 5 atm Po_2, while the oxidation of [U-^{14}C] glucose to $^{14}CO_2$ is markedly decreased, it is only logical that a major inhibition or inhibitions occur somewhere in or beyond the oxidation of pyruvic acid, as can be seen from the crude outline of glucose catabolism sketched in Figure 1. Only the reactions of direct interest to our problem are included in this sketch of the Krebs Cycle. In studying the problem with the aid of ^{14}C-labelled substrates, we have found two sites of special sensitivity to oxygen at high pressure. These were the oxidative decarboxylation of the two α-keto acids, pyruvic acid and α-oxoglutaric acid (α-ketoglutarate). Table IV provides an example of the inhibition of the oxidation of [1-^{14}C] pyruvate that occurs during a 30 minute incubation in oxygen at 5 atm. The addition of fumarate enables the acetyl CoA formed from pyruvate to enter the Krebs Cycle and increases the production of $^{14}CO_2$ at 1 atm Po_2. That the $^{14}CO_2$ production in oxygen at 5 atm does not completely follow suit would seem to indicate a later obstruction in the Krebs Cycle. This block was found to occur in the oxidative decarboxylation of α-oxoglutarate, as can be seen from Table V. At 5 atm Po_2, the production of $^{14}CO_2$ from α-oxo [5-^{14}C] glutarate was reduced within 30 minutes to 45-70% of control values of $^{14}CO_2$ produced at 1 atm. Po_2, a magnitude of inhibition comparable to that seen with [1-^{14}C] pyruvate. The oxidation of ^{14}C-labelled succinate was not significantly impaired during 30 minute incubations with oxygen at 5 atm.

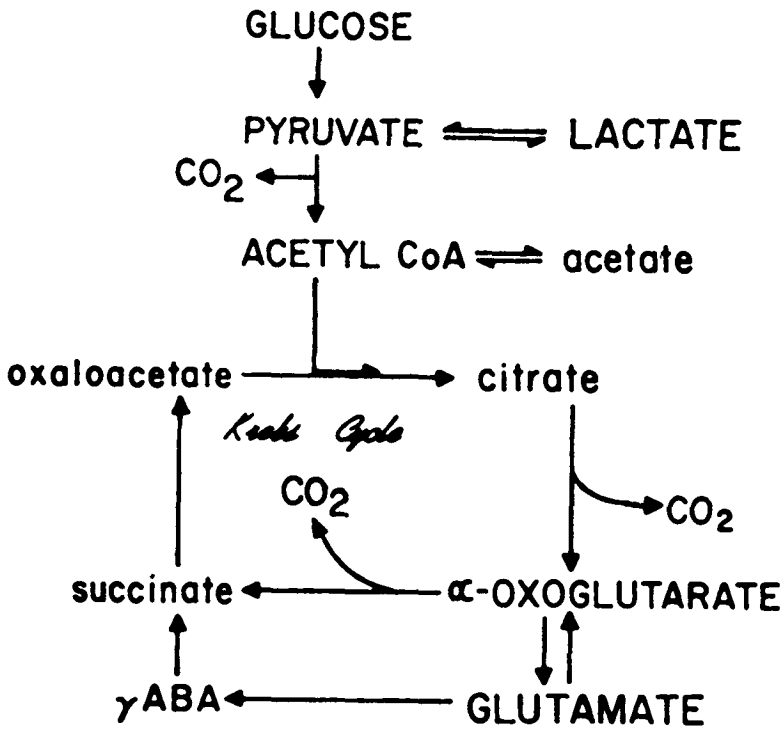

Figure 1. General Outline of Glucose Catabolism

The activity of pyruvic oxidase and α-oxoglutarate dehydrogenase was next evaluated more specifically in mitochondria prepared from rat brain during incubations in oxygen at 1 and 5 atm pressure. Through certain biochemical manipulations (by not adding adenosine triphosphate and by coupling the reactions to an oxygen-resistant system that required DPNH), the reactions could be confined to those specifically concerned with either of these two enzyme systems. Again, the highly sensitive and reliable measurements of the production of $^{14}CO_2$ provided the principal analytic tool.

In Table VI we can see an example of the rapid depression of the activity of pyruvic oxidase that occurred during incubation in oxygen at 5 atm. The marked decrease in the production of CO_2 from carbon-1 of pyruvate was most striking during this 15 minute incubation. The production of acetyl CoA from pyruvate was also depressed with oxygen at 5 atm. It was later shown that inhibitions such as these could be relieved by reducing the Po_2 to 1 atm.

Likewise, the activity of mitochondrial α-oxoglutarate dehydrogenase was quite rapidly depressed by oxygen at 5 atm, as is shown in Table VII by the decreased production of CO_2 from carbon-1 of α-oxoglutarate. The partial protection effected by dilute (2×10^{-4} M) KCN in this experiment as well as in those with pyruvic oxidase is particularly interesting, though not clear. One

TABLE IV

Oxidation of [1-^{14}C] Pyruvate by Cell-free Rat Brain Homogenate, and the Effects of the Addition of Four-carbon Dicarboxylic Acids

Po_2 (atm)	Fumarate Concentration in mM	Malate Concentration in mM	Counts/min in $^{14}CO_2$	Calculated μmoles of CO_2 from C-1 of Pyruvate
1	0	0	8,633	1.73
5	0	0	5,020	1.00
1	5	0	12,994	2.60
5	5	0	5,840	1.17
1	0	5	11,138	2.23
5	0	5	5,194	1.04

20 μmoles of [1-^{14}C] pyruvate containing 100,000 counts/min were incubated in 2 ml of cell-free rat brain homogenate for 30 min at 37° C and pH 7.4. Results are the means of closely agreeing duplicates.

TABLE V

Oxidation of α-oxo-[5-^{14}C] Glutarate and [1,4-^{14}C] Succinate

Substrate	Po_2 (atm)	Counts/min in $^{14}CO_2$ Produced	Per Cent Control $^{14}CO_2$
[5-^{14}C] α-oxoglutarate	1	$1997 \pm 2^{(3)}$	100
	5	$1013 \pm 44^{(3)}$	51
[1,4-^{14}C] succinate	1	$7427 \pm 192^{(3)}$	100
	5	$7076 \pm 1046^{(3)}$	95

16.25 μmoles of each substrate contained 100,000 counts/min at the labelled position. Incubations were for 30 minutes at 37° C at 1 and 5 atm Po_2.

TABLE VI

Mitochondrial Pyruvic Oxidase Activity was Measured by $^{14}CO_2$ Production from [1-^{14}C] Pyruvate during a 15 Minute Incubation at 37° C

Po_2 (atm)	Counts/min in $^{14}CO_2$ Produced	Minimal Calculated μmoles of CO_2 from C-1	Per Cent of Control
1	$4200 \pm 348^{(3)}$	2.10 ± 0.17	100
5	$473 \pm 112^{(4)}$	0.24 ± 0.04	11

50 μmoles of pyruvate were initially labelled at C-1 with 100,000 counts/min.

TABLE VII

Activity of α-oxoglutarate Dehydrogenase in Rat Brain Mitochondria

Po_2 (atm)	KCN Concentration in mM	Calculated μmoles of CO_2 from C-1 of α-oxoglutarate	Per Cent of Control $^{14}CO_2$
1	0	$2.29 \pm 0.02^{(3)}$	100
5	0	$0.34 \pm 0.18^{(3)}$	15
1	0.2	$2.54 \pm 0.10^{(3)}$	100
5	0.2	$2.15 \pm 0.02^{(3)}$	85

Incubation was for 30 minutes at 37° C and pH 7.4.

should recall that Riggs observed that dilute cyanide prevented the acute loss of tonus in isolated pyloric sphincter muscle that usually occurred during exposure to hyperbaric oxygen[22].

The close similarity of the two enzyme systems that appear to be most rapidly inhibited by oxygen at high pressure has stimulated us to make a hypothesis which appears quite reasonable. The rather complicated Figure 2 outlines steps that may be considered to occur during the oxidative decarboxylation of pyruvate[23], but the same general scheme holds for the oxidative decarboxylation of the other α-keto acid, α-oxoglutarate. The two systems require the same cofactors: Mg^{2+}, thiamin pyrophosphate, coenzyme A, and a dithiol compound, α-lipoic acid. With pyruvic oxidase, the decarboxyation of carbon-1 is markedly depressed with oxygen at 5 atm. The oxygen induced inhibition has not been relieved by the addition of excess amounts of Mg^{2+}, CoA, or thiamin pyrophosphate,

PYRUVIC OXIDASE

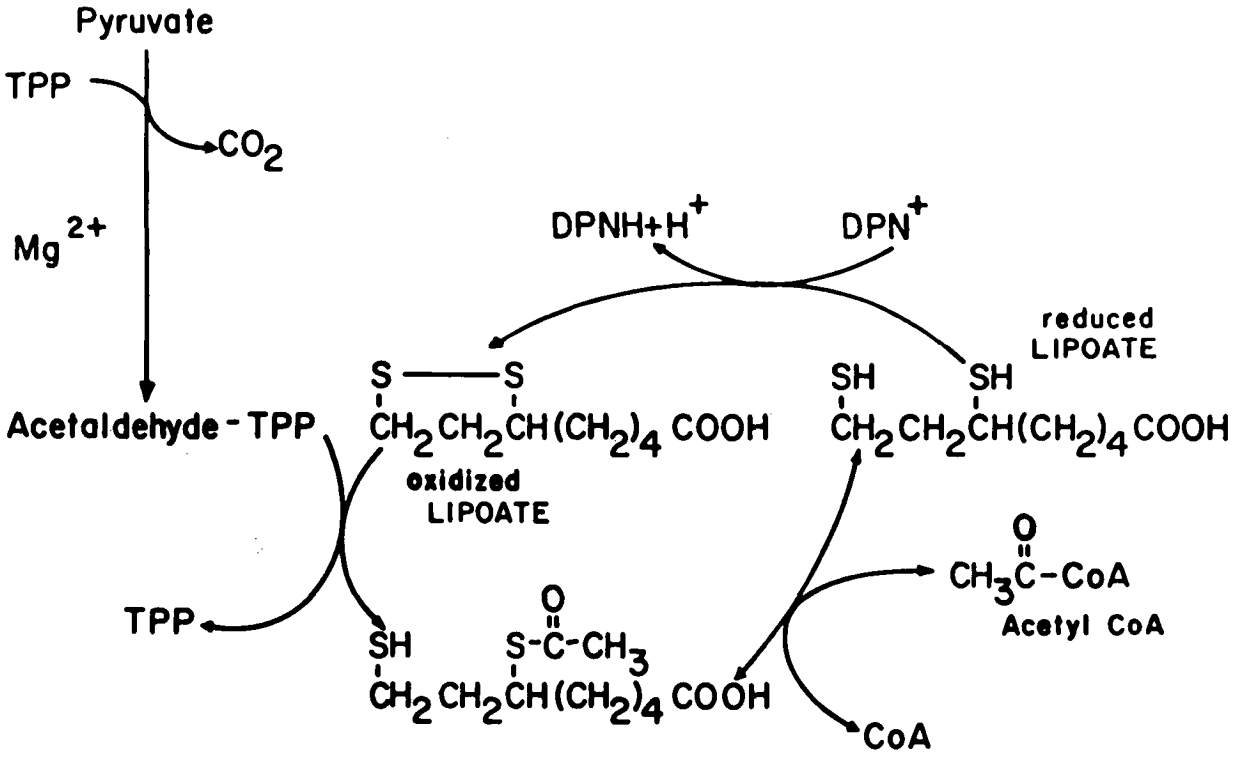

Figure 2. Mechanisms in Pyruvic Oxidase

which leaves us with a α-lipoic acid as the likely site for the effects of oxygen. It can be seen that the two-carbon fragment resulting from the decarboxylation of pyruvate must be transferred and oxidized by α-lipoic acid while en route to the formation of acetyl CoA. In accomplishing this transfer the two thiol groups of α-lipoic acid must first be reduced, and then oxidized by DPN^+. If this operation is prevented, as by oxidation with a divalent heavy metal (or metalloid such as the organic arsenical lewisite), the oxidative decarboxylation of pyruvate will be blocked. The failure of the monothiols GSH and cysteine to protect the rapid changes in this particular system is not surprising, for it has frequently been shown that only dimercaptans with contiguous thiol groups can prevent or reverse the action of heavy metals on this system[24]. More definitive proof of this mechanism will be difficult since α-lipoic acid is enzyme-bound and the popular dithiol agent BAL is itself rapidly oxidized by high oxygen pressure.

Other workers have found inhibition of the oxidation of pyruvate with oxygen at high pressure which occurred more slowly[2]. Recently, inhibitions of the oxidation of both α-keto acids have been produced by oxygen in bacteria (Azotobacter vinelandii)[25]. These inhibitions were both rapid and reversible and can be interpreted as using a mechanism similar to that proposed by us.

A rapid and reversible inhibition of the oxidative decarboxylation of these two α-keto acids by oxygen at high pressure certainly provides an attractive hypothesis to explain the acute neurologic disturbances in the intact animal. The key positions of these two compounds and their reactions in both the energy metabolism and the amino acid metabolism of the brain is quite apparent. Even small disturbances of either enzyme system could produce widespread biochemical aberrations. For example, such a mechanism would adequately explain the fairly rapid impairment (50% in 90 minutes) in K^+ and Na^+ transport in slices of guinea pig cerebral cortex incubated at 6.6 atm Po_2 as reported by Kaplan and Stein[26]. Such an impairment of sodium extrusion from neurons and their dendrites in the intact brain would result in a gradually increasing depolarization that could lower their convulsive threshold so that minimal or even normal stimuli might initiate a seizure discharge[27]. The occurrence of such neurochemical aberrations in even very small and localized regions of the brain, though imperceptible in measurements of brain O_2 consumption, could produce most of the excitatory neurologic phenomena seen in vivo.

Despite the attractiveness of this theory, it lacks positive proof both in vitro and in vivo. We do not believe that our results really disagree with the data previously found with the respiration of brain slices[3,4,5], and hope to demonstrate this, again through the use of ^{14}C-labelled substrates. However, the conclusive evidence must be provided by measurements on the intact brain of the live animal. The brain is an organ that is notoriously inaccessible to adequate research in vivo at the enzyme level, particularly because of the blood-brain barrier. We do propose, however, that much valuable information can be gained from studies of the metabolism of uniformly ^{14}C-labelled glucose in the brains of perfused animals or intact subjects exposed to hyperbaric oxygen.

We do not propose that such a simple mechanism as outlined above can account for all of the toxic effects of oxygen at high pressure. As mentioned, many other enzymes, particularly -SH dependent ones are slowly and irreversibly

inactivated by hypernormal concentrations of oxygen and correlate better with the more slowly developing but irreversible toxic effects in the intact animal, such as the lung pathology. In this type of enzyme poisoning, it is more likely that the protein apo-enzymes are inactivated, and not the more resilient cofactors, which can be replenished or reactivated much more easily and quickly.

Inactivation of enzymes by the oxidation of essential sulfhydryl groups has often been proposed as the mechanism for oxygen toxicity on the basis of many experiments in vitro[2,28]. In vivo, the importance of -SH groups and their inactivation by oxygen at high pressure has been well documented by Gerschman and her co-workers[29,30,31]. These investigators observed significant protection against the lethal effects of oxygen at 6 atm in mice given reagents which contained sulfhydryl groups, such as cysteamine, cysteine, BAL, or reduced glutathione (GSH). On the basis of a similar protection by these reagents against x-irradiation in mice, as well as possible synergistic effects of hyperbaric oxygen combined with radiation, it was proposed that these very different agents act by a common mechanism[29,30,31]; that is, that both hyperbaric oxygen and x-irradiation act in tissues through the formation of oxidizing free radicals, particularly peroxides. Unfortunately, no direct experimental evidence has yet been found which supports this interesting theory. Moreover, conflicting results were obtained in the studies mentioned, for the above "sulfhydryl-protecting" reagents were detrimental rather than helpful at oxygen pressures of from 1 to 1.5 atm. It should be recalled that no peroxides were detected by Dickens in rat brain (slices or homogenates) incubated for two hours with hyperbaric oxygen[5]. Also, the addition of catalose, which should destroy hydrogen peroxide, has proven ineffective against the effects of oxygen in vitro[20,25].

Guzman Barron[32] has found that many non-protein sulfhydryl groups such as those of reduced glutathione (GSH), cysteine and coenzyme A (CoA) are rapidly oxidized in neutral aqueous solutions at high oxygen pressure (17 atm Po_2 for 20 minutes). He expressed the view that the effects of hyperbaric oxygen and x-irradiation are similar only in their effects upon -SH groups, but not in their mechanisms. X-irradiation acts through the ionization of water in forming the highly reactive free-radicals $\cdot OH$ and $\cdot O_2H$ which can easily form peroxides and oxidize -SH groups. Guzman Barron proposed that oxidation of -SH groups by hyperbaric oxygen is performed through complexes formed by oxygen with heavy metal ions such as ferric (Fe^{3+}) or cupric (Cu^{2+}) ions. This latter viewpoint which stresses the role of heavy metal ions is particularly interesting in view of Haugaard's recent experiments with the toxic effects of oxygen on the oxidation of glucose by heart homogenates[33]. Haugaard and his co-workers found that trace amounts of cupric ions greatly accentuated the toxic effects of oxygen at 1 atm, whereas the chelating agent Versene (EDTA) protected against the toxic effects of oxygen. However, EDTA has provided only partial protection against the effects of high oxygen pressure in our experiments.

Thus the exact physicochemical mechanism whereby sulfhydryl groups are inactivated by hyperbaric oxygen is not at all clear. Oxidation by free radicals probably is involved, since the "one-step" oxidation-reduction reactions in biological systems implicitly must involve free radical intermediates[31]. The step from molecular oxygen to the formation of oxidizing free radicals is a very big one, however. The oxygen molecule does have two unpaired electrons and may

be regarded as sort of "diradical." Although it is not sufficiently reactive to attack most organic molecules, oxygen is very adept at combining with free radicals that have already been formed[34]. For this, the ferric or cupric ions may suffice, as previously suggested[30].

Besides this mechanism, hydroperoxy radicals can be formed by the addition of molecular oxygen to organic radicals which have previously been formed. Such hydroperoxy radicals are far more reactive than is molecular oxygen and could rapidly oxidize -SH groups and conceivably might even initiate chain reactions. The problem, then, would be to find out which organic radicals in particular would be likely to add molecular oxygen. A possible site would occur in the respiratory chain of cytochrome enzymes, which are continually being oxidized and reduced. This speculation might explain the "protective" effects shown by dilute cyanide.

SUMMARY

In summary, it may be concluded that the chemical mechanisms of oxygen toxicity are intimately concerned with the inactivation of enzyme systems. Two types of inhibition by oxygen seem to be concerned:

1) Slow and irreversible inactivation of certain enzymes by the effects of oxygen acting directly upon the protein apo-enzymes themselves. This may be related to the slowly fatal and irreversible effects of oxygen in vivo.

2) The rapid and reversible inhibition of specific enyzmic systems by the action of hyperbaric oxygen on essential cofactors such as α-lipoic acid. This would be related to the reversible neurotoxic effects in vivo. In both types of inhibition, the oxidation of essential -SH groups is usually involved.

On the basis of our recent work, a mechanism for the acute neurotoxic effects of hyperbaric oxygen may be proposed, which involves the rapid and reversible inhibition of two key enzymes, pyruvic oxidase and α-oxoglutarate dehydrogenase. This working hypothesis certainly requires much further investigation, in vivo and in vitro.

The exact physicochemical mechanisms whereby -SH groups are inactivated by hyperbaric oxygen are still speculative, although free radical intermediates are very likely.

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THE HISTOCHEMICAL EFFECTS OF OXYGEN AT HIGH PRESSURES

N. H. Becker and C. H. Sutton
Laboratory Division, Montefiore Hospital, New York

The problem of oxygen toxicity has assumed renewed importance in view of the artificially constructed atmospheres proposed for use in both space and undersea explorations. Since the pathogenesis of this oxygen effect is poorly understood, it seemed desirable to reinvestigate the problem at a histochemical level.

A study of cerebral lipid peroxides (CLP) seemed promising since Wollman[1] had demonstrated an increase of lipid peroxides in the brains of rats following exposure to oxygen at high pressures (OHP). It had been shown earlier, that lipid peroxides were capable of inhibiting many enzymes[2,3,4,5], and were responsible for some of the effects of radiation damage[6,7,8]. Indeed, the high fat content and ordered molecular structure of the brain lipids suggested that lipid peroxide formation might represent an important toxic effect of hyperoxia.

In order to explore the limits and significance of this OHP effect on the CLP, adult rats were exposed at various pressures of 100% oxygen until approximately 50% underwent convulsive seizures. They were killed immediately upon surfacing and the brains taken for estimation of CLP. Since adrenalectomy had been shown to delay the onset of oxygen convulsions[9], the effect of adrenalectomy on the CLP was included in these studies. The experimental conditions and findings are summarized in Table I[10].

TABLE I

EFFECT OF OXYGEN ON CEREBRAL LIPID PEROXIDES

Procedure	Number Animals	Standard Deviation	Lipid Peroxide Units/Gm Mean
Normal unexposed rats	64	15.5	56.4
Exposed 2-3 hours in O_2 at 165 feet	15	11.8	69.5
Exposed 4-6 hours in O_2 at 132 feet	39	23.1	80.9
Exposed 4-6 hours in O_2 at 99 feet	26	17.7	72.0
Exposed 4-6 hours in O_2 at 66 feet	15	15.8	68.0
Exposed 6-8 hours in O_2 at 33 feet	28	11.0	59.8
Exposed 48 hours in O_2 at sea level	12	10.5	57.5
Exposed 72 hours in O_2 at sea level	7	7.1	54.3
Exposed 11 hours in air at 200 feet	9	10.4	56.6
Unexposed, Sham-adrenalectomized	6	5.9	51.2
Unexposed, Adrenalectomized	6	4.3	43.0
Exposed, Sham-adrenalectomized, in O_2 at 132 feet, 4-6 hours	12	15.9	56.8
Exposed, Adrenalectomized, in O_2 at 132 feet, 4-6 hours	22	14.7	62.3

It was noted that significant elevations in CLP occurred in rats exposed to OHP. This effect disappeared at and below 33 feet (14.7 psi). The elevations of CLP did not differ between the convulsing and non-convulsing animals. Although convulsions were noted at 33 feet, they were unaccompanied by elevations of CLP. Adrenalectomy delayed somewhat the onset of convulsions, while the CLP did not rise above that of normal unexposed animals. The inhibitory effect of a sham adrenalectomy on the elevation of CLP by OHP and the abolition of this effect by adrenalectomy remained unexplained. These sham operated animals convulsed as readily as normal animals. Similarly unexplained was the lowering of the CLP level in the unexposed adrenalectomized rats.

One concluded that the CLP elevations were not a factor in oxygen convulsions. Of course, the possibility existed that focal increases in CLP, not reflected in the total brain estimations, could have served to trigger a seizure.

In a further attempt to study the histochemical effects of hyperoxia, adult rats were exposed to OHP (200 feet 103 psi absolute) for 30-45 minutes until convulsions ensued. Most animals were killed immediately upon surfacing, while a few were permitted to survive eight hours before study. Another group was exposed to 100% oxygen at atmospheric pressure and the animals were killed after oxygen exposure of 24, 48 and 72 hours, respectively. The brains and lungs were taken for both routine histological and special histochemical studies.

Routine histological examinations revealed the following picture: In rats killed immediately after exposure to OHP, the brains appeared normal. The lungs were the seat of a moderately severe pulmonary edema (Figure 1). The alveoli were filled with fluid and occasional fresh red blood and mononuclear cells. Perivascular and peribronchial edema was common. There was considerable dilatation of the capillaries (Figure 2). The tracheobronchial tree was normal. In the animals surviving eight hours, no abnormalities could be found in the brain. The pulmonary edema had subsided but, often, an increased number of interstitial mononuclear cells were present (Figure 3).

The brains and lungs of rats exposed to 100% oxygen at atmospheric pressure for 24 hours were normal when studied in routine histological sections. Similarly, the brains of animals exposed for 48 hours were normal. However, there was moderately severe pulmonary edema similar to that seen in the OHP cases (Figure 4). In animals exposed for 72 hours, focal clusters of neurons exhibiting acute cell change were seen in the neocortex, thalamus and cerebellum of almost one-half the exposed rats. The pulmonary edema in all these rats had progressed to such an advanced degree (Figure 5) that these animals were in a terminal state characterized by severe dyspnea and often, stupor.

The recent development of relatively simple enzymatic staining techniques for the visualization of various intracellular organelles[11,12] (e.g., lysosomes, mitochondria, Golgi apparatus), as well as the enzymatic activity of blood vessels, provided somewhat more sophisticated tools with which to explore the effects of hyperoxia.

Earlier cytochemical studies of the effects of anoxia on the rat brain[13,14,15] had shown progressive swelling and ultimate loss of neuronal lysosomes and mito-

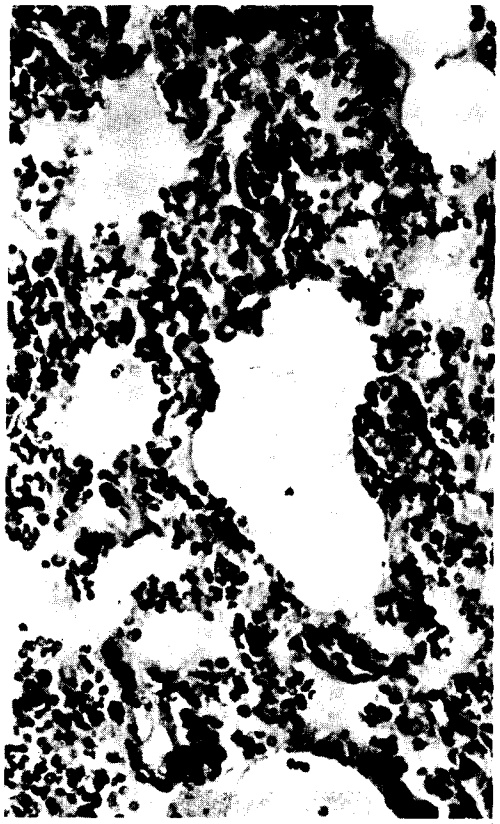

Figure 1. Lung: Rat was killed upon surfacing from exposure to oxygen at 200 ft (103 psi absolute) for 40 minutes. Note exudation of fluid, red blood and mononuclear cells into the alveolar spaces. H E x 250.

Perkinje cells of the cerebellum (Figure 6). Occasionally swollen mitochondria were seen.

In the brains of rats exposed to oxygen at atmospheric pressure for 24 hours, no cytochemical changes were seen. However, from 48 to 72 hours, both swelling and loss of neuronal lysosomes were seen in the neocortex and the Purkinje cells (Figure 7). There was also swelling and loss of neuronal mitochondria as well as fragmentation and loss of the Golgi apparatus. Many of these changes, particularly those of lysosome, occurred before they could be detected in routine hematoxylin-eosin and Nissl preparations.

In describing the foregoing cytochemical responses to hyperoxia, only the abnormal findings will be presented. The brains of rats killed immediately after convulsions in OHP revealed no abnormalities. However, in the animals that were permitted to survive eight hours, scattered foci of neurons with swollen lysosomes were found in the neocortex, thalamus and the

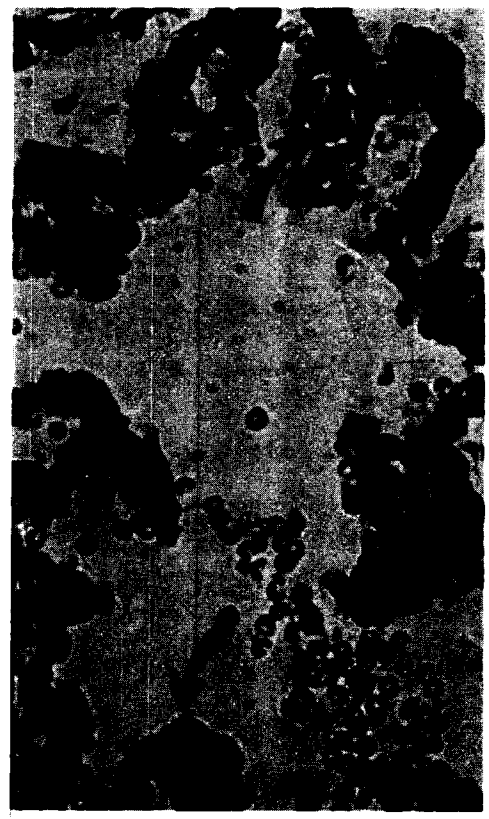

Figure 2. Lung: Same animal as Figure 1. Note Capillary dilatation in the walls of the alveoli (arrows) PAS x500.

chondria (Figure 8) and fragmentation and loss of the neuronal Golgi apparatus (Figure 9).

Since these cytochemical responses of neurons to hyperoxia were no different from that seen in other necrobiotic processes, one must conclude that these alterations were secondary to a more fundamental, yet undisclosed, effect of hyperoxia. It is noteworthy that the distribution of these altered neurons was similar to that seen in anoxia[13,14,15].

Figure 3. Lung: Rat was killed eight hours after surfacing from exposure to oxygen at 200 ft (103 psi absolute) for 45 minutes. No exudate is present in the alveoli. Focal atelectasis and an increased number of interstitial round cells are noted. H E x250.

Figure 4. Lung: Rat was killed after 48 hours exposure to 100% oxygen at atmospheric pressure. Note the perivascular edema. H E x150.

In the lungs of rats sacrificed immediately after exposure to OHP, the acid phosphatase staining for lysosomes revealed an increased number of histiocytes in the walls of the alveoli (Figure 10). These histiocytes were easily visualized by virtue of their high acid phosphatase activity. This histiocytic infiltration was more prominent after eight hours (Figure 11). The mitochondria were unaltered.

After 24 hours of exposure to oxygen

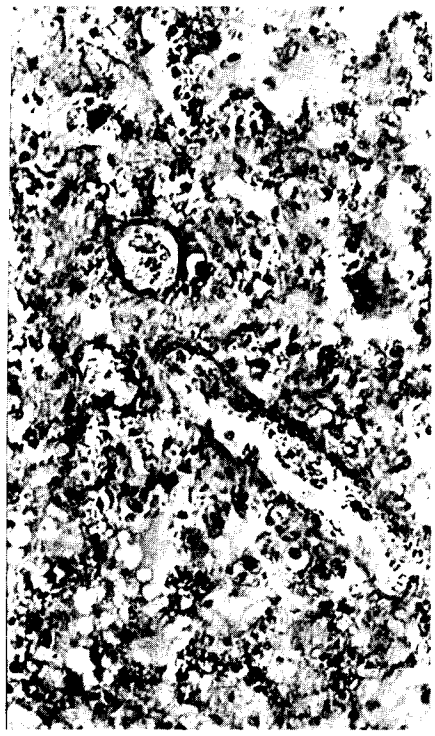

Figure 5. Lung: Rat was killed after 72 hours exposure to 100% oxygen at atmospheric pressure. Note the extensive pulmonary edema and vascular dilatation. H E x150.

Figure 6. Cerebellum: Same rat as Figure 31. Swollen lysosomes are present within many Purkinje neurons (arrows). Compare with normal neurons (N). Acid phosphatase, 30 minute incubation. x 700.

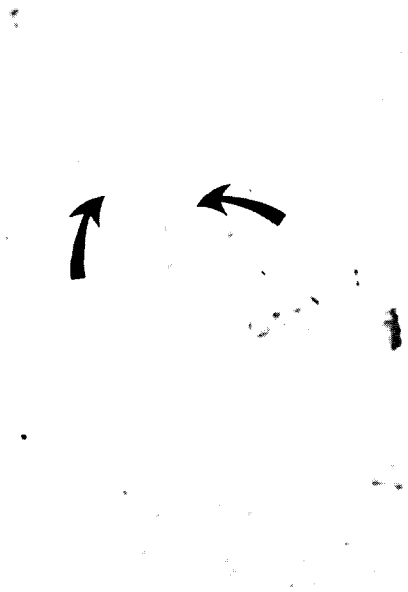

Figure 7. Cerebellum. Same rat as Figure 5. Note absence of lysosomes in the Purkinje cells (arrows). Acid phosphatase, 30 minute incubation. x700.

at atmospheric pressure, the histiocytic infiltration of the lung became increasingly prominent. In addition, there was an increased number of lysosomes in the alveolar cells (Figure 12). In the 48-72 hour group, clusters of alveolar cells with swollen mitochondria were seen as well (Figure 13).

The increased number of histiocytes and alveolar cell lysosomes, as well as the swollen mitochondria, are not unique to the oxygen effect but could have represented a common response to the exudative reaction. The lysosomal change could also have reflected an increased pinocytotic behavior of the alveolar cells.

The most impressive enzymatic activity of normal lungs was that of adenosine triphosphatase and thiamine pyrophosphatase. With both substrates, the major activity was noted in the endothelial cells of both the larger and smaller blood vessels. As a result, the alveolar walls are well stained (Figure 14). In focal zones of endemic murine pneumonitis, there was diminished or absent staining of these vessels (Figure 15).

In the rats killed immediately after exposure to OHP, the zones of exudative reaction were associated with a loss of the adenosine triphosphatase and thiamine pyrophosphatase activity from the blood vessels (Figure 16). Similar losses were present in rats after 24-72 hours in oxygen at atmospheric pressure. However, no such losses were present in animals surviving eight hours after exposure to OHP.

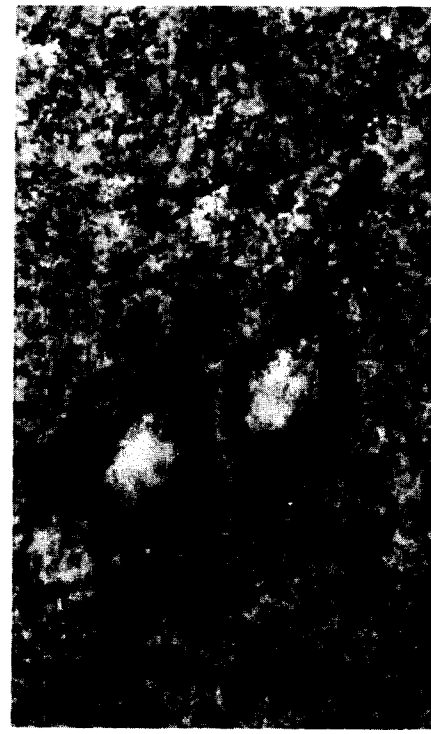

Figure 8. A. Neocortex: Normal rat. Compare normal size of mitochondria in neurons (arrows) with 5B. x700.

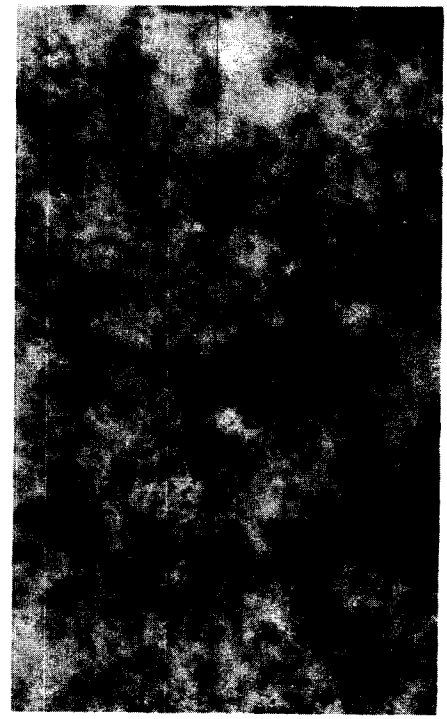

Figure 8. B. Neocortex: Same rat as Figure 5. Note swollen mitochondria (arrows), as well as neurons with loss of mitochondria (L). DPNH-diaphorase, 30 minute incubation. x700.

Figure 9. A. Neocortex: Normal rat. Compare normal Golgi Lamellae in neurons (arrows) with 9B. x 700.

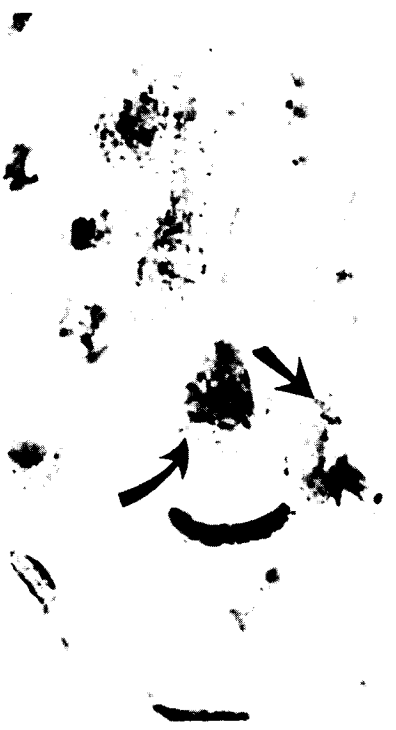

Figure 9. B. Neocortex: Same rat as Figure 5. Note fragmentation of the Golgi lamellae in small granules (arrows). Thiamine pyrophosphatase, 20 minute incubation. x700.

Figure 10. A. Lung: Normal rat. Note the acid phosphatase-rich histiocytes (arrows) scattered through the alveolar walls. x250.

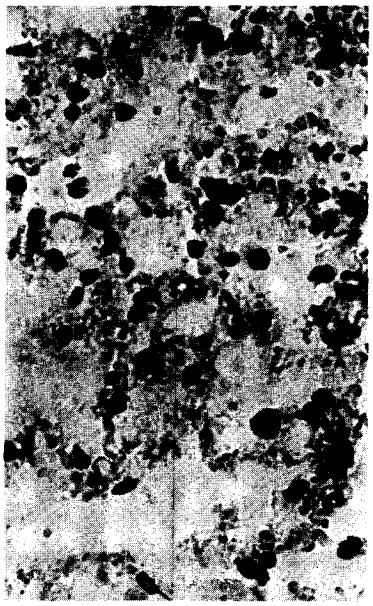

Figure 10. B. Lung: Same rat as Figure 1. Note the increased number of histiocytes some of which are free in the alveolar spaces. Acid phosphatase, 30 minute incubation. x 250.

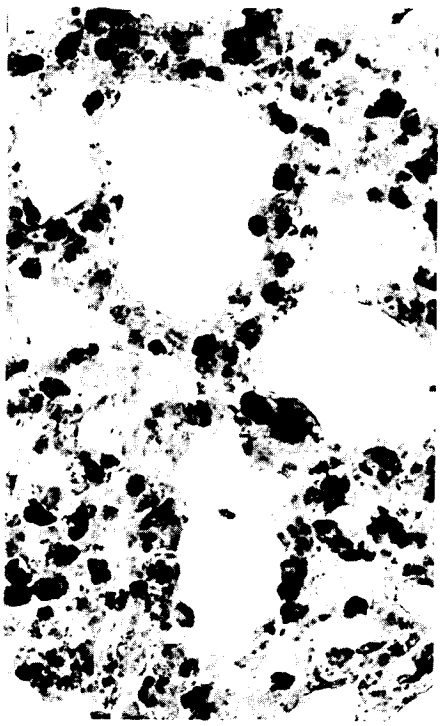

Figure 11. Lung: Same rat as Figure 3. Note the large number of histiocytes in the alveolar walls. Acid phosphatase, 30 minute incubation. x 250.

Figure 12. A. Lung: Normal rat. Note occasional lysosomes present within the alveolar walls (arrow). x 500.

Figure 12. B. Lung: Rat killed after 24 hours exposure to oxygen at atmospheric pressure. Note the increased number of lysosomes (arrow) in some of the alveolar cells. Acid phosphatase, 30 minute incubation. x500.

Figure 13. Lung: Rat killed after 48 hour exposure to oxygen at atmospheric pressure. Note the swollen mitochondria (arrows) in the alveolar cells. The smaller granules represent mitochondria of normal size. DPNH-diaphorase, 50 minute incubation. x 500.

Figure 14. Lung: Normal rat. There is intense staining of the alveolar walls due to the high level of polyphosphatase activity in the endothelium. Note the endothelial staining of a small arteriole (arrow). ATPase, 20 minute incubation. x100.

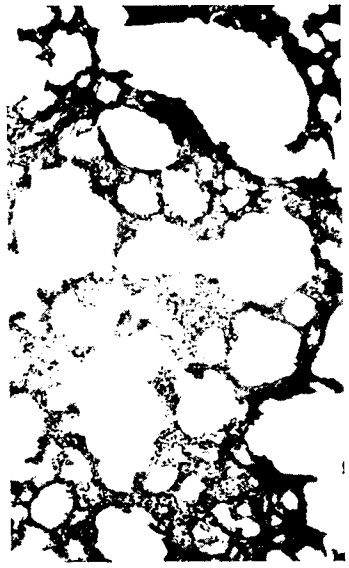

Figure 15. Lung: Normal rat. Note the focal loss of staining in zones of murine pneumonitis. ATP-ase, 20 minute incubation. x100

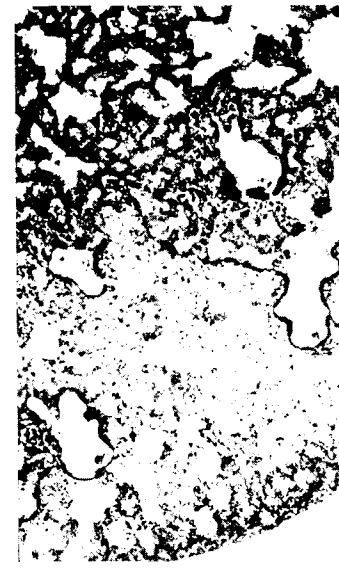

Figure 16. Lung: Same rat as Figure 1. Note loss of staining in the subpleural zone of pulmonary edema. ATP-ase, 20 minute incubation. x100.

In summary, the loss of the polyphosphatase activity in the pulmonary vessels and the influx of histiocytes, as demonstrated by acid phosphatase activity, appeared to be the most consistent and extensive response to hyperoxia. The increased number of alveolar cell lysosomes and the swelling of the mitochondria were usually less extensive and occurred relatively late in the course of the exudative process.

It must be re-emphasized that none of the histochemical changes reported here were unique to oxygen toxicity but could be seen in other necrobiotic processes. These techniques have been useful in suggesting that, at least histochemically, there is nothing particularly unique about the toxic effect of oxygen. A more sophisticated interpretation of this data must await a fuller understanding of the general cytochemical pathology of these organs.

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BREATHING OF PRESSURE-OXYGENATED LIQUIDS

J. H. Pegg, T. L. Horner and E. A. Wahrenbrock
Cardiovascular Research Institute and Department of Anesthesia
University of California Medical Center
San Francisco, California

Since the solubility of a gas in a liquid is directly proportional to the applied partial pressure (Henry's Law), it is possible with sufficient pressure to dissolve an arbitrarily great amount of oxygen in a physiologic liquid. In particular, normal saline at 37° C equilibrated with oxygen at 10 atmospheres absolute contains in solution 20 volumes per cent oxygen, approximating air at sea level in oxygen content. If, despite its enormous density and viscosity, sufficient alveolar ventilation could be obtained breathing such a pressure-oxygenated liquid, mammalian life might be sustained in a totally liquid environment. Indeed there are early, unpublished observations by Haldane, who accidentally discovered delayed drowning of mice in water of high oxygen tension. Levine and Coryllos[1] submerged dogs in liquids with approximately 2 atmospheres oxygen tension and noted survivals up to one-half hour, although the animals died of aspiration pneumonia on return to air breathing. Last year Kylstra[2] reported survival of mice for up to 18 hours breathing a balanced and buffered salt solution at 20° C, equilibrated with oxygen at 8 atmospheres. On removal the mice lived little over two hours. More recent work by Kylstra[3] has demonstrated that submerged, intubated dogs in a pressure chamber at 4 atmospheres of air with supplementary oxygenation by intravenous oxygen insufflation survived for a period lasting as long as four weeks. As much liquid as possible was drained from the lungs with suction through an endotracheal tube prior to their removal from the chamber.

METHODS AND OBSERVATIONS

Under ether anesthesia, 33 rats were tracheostomized, tied to a lucite frame, and after electrocardiographic leads were fitted (an iliac arterial catheter was inserted in some rats), the rats were placed erect in a pressure chamber flushed with oxygen through a sintered bubbler at the bottom (Figure 1). The chamber was partially filled, submerging the animal in an isotonic solution at 37° C. The lid was bolted on an oxygen bubbled in rapidly from a pressure-regulated supply, the flow rate being controlled by an outlet valve at the top. Desired pressure was attained within two minutes after immersion, and solution Po_2 as monitored by oxygen electrode[4], reached equilibrium within three minutes at pressure. Solution temperature was held between 33° - 37° C. With 16 rats, a solution balanced in ionic concentration and osmolarity with rat plasma was used (Na^+ 142, K^+ 6.3, Ca^{++} 6.1, Mg^{++} 2.3, Cl^- 130, HCO_3^- 26, $H_2PO_4^-$ 0.5 mEq/l. and 0.1% glucose). Upon immersion some of the oxygen in the rats' lungs was expired. The remaining oxygen, being compressed by chamber pressurization, was absorbed by the blood stream. If none of the lung oxygen escaped and all were compressed into alveoli, it should all be metabolically consumed within five minutes.

Upon immersion of the tracheostomy tube the heart rate dropped approximately 40 per cent in five rats (control rate of 420/min), consistent with a bradycardia reported in other submerged mammals[5]. In the same rats, irregular

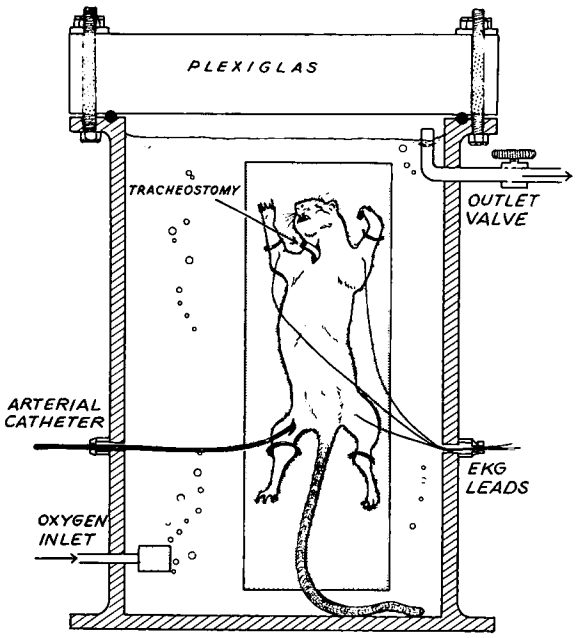

Figure 1. Chamber for Breathing of Pressure Oxygenated Liquids.

respiration during the first three minutes gave way to a respiratory rate of approximately 28/min (control rate 69/min) with prolonged (75% of cycle) forced expiration. Skin and mucous membranes were pink and remained so, presumably due to direct oxygen diffusion from the solution, even after death (judged by cessation of respiratory movements and an electrocardiographic rate less than 60/min). Survival time was less than five minutes at 2.5 atm (two rats), rose to 170 and 248 min at 10 atm (two rats), and dropped to 90 and 135 min at 20 atm (two rats). At 10 atm, one rat breathing distilled water, two breathing sea water, and two without tracheostomy breathing isotonic solution died within seven minutes. After 30 minutes breathing the balanced solution at 10 atm (one rat), arterial oxygen saturation was 76%, Pco_2 174 mm Hg, and pH 6.61. The high Pco_2 (normal 40 mm Hg) indicated the poor CO_2 carrying capacity of this virtually unbuffered solution. Six other animals were immersed in a solution buffered with 0.4% THAM[6] plus Na^+ 123, K^+ 6.2, and Cl^- 129 mEq/l. After 30 minutes in this solution at 10 atm (one rat), Pco_2 was 50 and pH 7.00. With a 15-minute equilibration period between each increase in pressure, arterial saturation in another rat was 24% at 10 atm, 49% at 12.5 atm, 79% at 15 atm, 93% at 17.5 atm, and greater than 100% (sample foamed) at 20 atm. Metabolic acidosis (pH 7.14, Pco_2 34 at 10 atm) decreased with increasing saturation (pH 7.28, Pco_2 45 at 17.5 atm). In the buffered solution at 15 atm, two rats, unrestrained in the chamber but kept below the surface by a screen, showed normal motor activity in response to bright light by tapping on the chamber wall and changes in position of the chamber.

After 30 minutes the liquid, rapid decompression (30 sec), removal from the chamber, and postural drainage to remove most of the 5-7 ml of fluid in the lungs, eight rats quickly resumed normal breathing and had a normal gait. However, within 15 minutes, sero-sanguinous fluid with bubbles appeared in the transparent tracheostomy tube, respiration became slow and labored, mucous membranes were cyanotic, and the rats died despite administration of 100% oxygen or intermittent positive pressure breathing. When the chest was opened, the lungs collapsed completely and small pleural effusions were present. Lung extracts for pulmonary surfactant[7], done in five rats, had minimum surface tensions greater than 18 dynes/cm (normal less than 10 dynes/cm). Curiously, one of four rats immersed in normal saline for 30 minutes at 15 atm survived unassisted in air for two hours and another for more than seven hours; the latter's lungs had

hyaline membranes. Foam was found in the heart and arteries of three rats that died in the solution at 20 atm.

Death could be greatly delayed by continuous positive pressure breathing via T-tube on the tracheostomy (Figure 2), the animal continuing to ventilate spontaneously. With air at 7.5 cm H_2O pressure, one rat survived approximately three hours and at 15 cm H_2O, another approximately five hours. With 100 % oxygen, after 12 hours survival, weaning by gradual reduction in pressure was attempted in one rat. Tachypnea occurred when the pressure was reduced to 5 cm and persisted for three hours. Pressure was then reduced to 0 (at 16 hours), and the rat died within seven minutes. The lungs had hyaline membranes (Figure 3). Another rat maintained at 15 cm H_2O pressure with 100% oxygen survived over 21 hours; its lungs also had hyaline membranes. Prian[8] has subsequently shown that hyaline membranes produced in this manner stain positively with the PAS reagent. A control rat similarly tracheostomized, restrained, and given 15 cm H_2O continuous positive pressure with 100% oxygen survived only 12 hours; its lungs had no hyaline membranes.

DISCUSSION

Arterial blood gas measurements imply that alveolar ventilation was roughly half normal; nearly 20 atm (40 volume percent oxygen in solution) were needed to saturate the blood and Pco_2 was over four times normal, reflecting the decreased CO_2 carrying capacity of water (0.55 compared with air), hypoventilation, and the additional CO_2 produced from bicarbonate by metabolic acidosis. The labored respiration and acidosis seen in rats, even in the buffered solution, suggest that they succumb in the liquid from exhaustion from the excessive work of breathing. Breathing of pressure-oxygenated solutions is not innocuous, as demonstrated by the prompt death usually seen upon return to gaseous environment. Since the animal is totally submerged, it is subject to breathing contaminants (skin oils, urine, feces) which may damage the lungs. Perhaps retained liquid in the lungs is detrimental and the prolonged survival of the animals breathing saline resulted from its lack of effective oncotic pressure (provided by the glucose and THAM in the other solutions) permitting more rapid absorbtion from the alveoli. The collapse

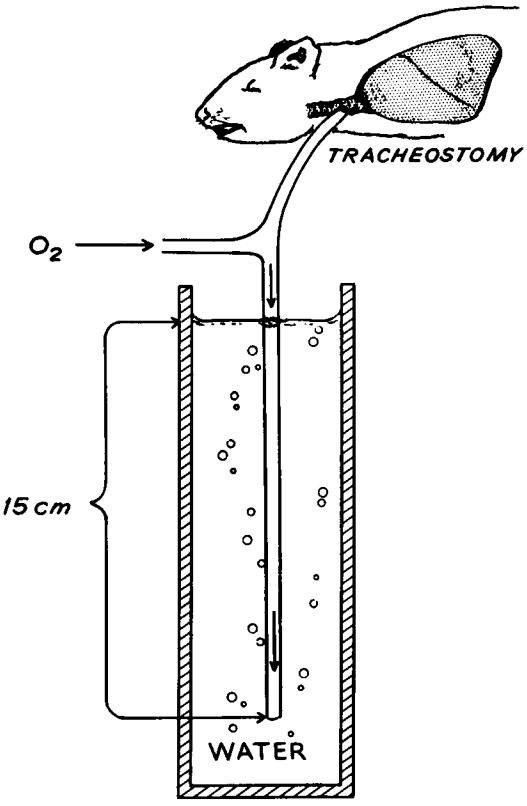

Figure 2. Continuous Positive Pressure Apparatus.

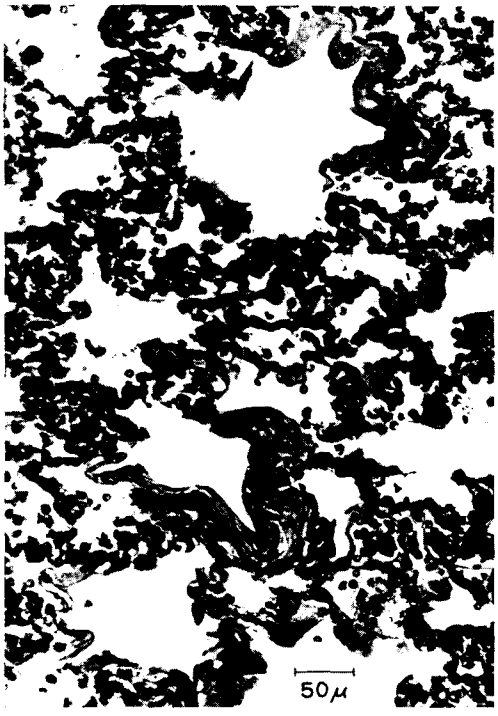

Figure 3. Photomicrograph of Rat Lung Showing Hyaline Membranes and Atelectasis 16 Hours after Breathing the Liquid.

of the lungs and abnormal surface tensions of lung extracts seen at autopsy of rats removed from the liquid, and their need for continuous positive pressure, suggests that death following air breathing is due to massive atelectasis, due to washing out of the pulmonary surfactant with consequent increase in surface forces tending to collapse alveoli. A deficiency of this material occurs in idiopathic respiratory distress syndrome of the newborn[9] in which PAS positive staining hyaline membranes are also found.

Further investigations on breathing of pressure-oxygenated liquids may clarify the changes taking place during the liquid to gas transition at birth, their complications, and possible therapy. Should this process be made completely innocuous and reversible, it is likely that man, himself, will choose to live temporarily in a liquid environment. This would permit diving to unlimited depths without decompression, inert gas narcosis (the inert gas being replaced by an inert liquid) or oxygen toxicity.

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PHYSIOLOGICAL EFFECTS OF OXYGEN

C. J. Lambertsen
Laboratories of Pharmacology
University of Pennsylvania
Schools of Medicine
Philadelphia, Pennsylvania

The vital relationship of oxygen to diving is often confused by two strange attitudes. On the one hand many investigators take this active agent for granted and therefore ignore it as a factor in production of the gross physiological changes which may accompany diving. Others, preoccupied with the ability of oxygen to produce toxicity, fail to exploit the considerable advantages which can result from breathing oxygen at increased pressures both in diving and during decompression after diving. From both a practical and a theoretical standpoint, oxygen has important effects which are distinct from toxicity and are unrelated to the relief of the anoxic state. In describing some of these effects here, primary attention will be given to ways in which oxygen inspired at high pressures may alter respiration.

The effects of oxygen will be discussed roughly in the order in which the inspired oxygen molecules reach the anatomical site of their physiological or pharmacological action. Beginning with the first breath, the list of non-toxic effects on respiration is shown in Table I.

PHYSICAL EFFECTS OF HIGH OXYGEN PRESSURES ON THE LUNGS

Certainly, as described in the session on Respiratory Effects of Increased Ambient Pressure, the nature of the inert gas vehicle which carries the oxygen breathed at high ambient pressures can affect the dynamics of alveolar ventilation when total ventilation is high[1,2,3]. It also appears true that oxygen must be delivered at a higher pressure than nitrogen to provide a desired flow through an orifice[4]. The relationship of this property to the over-all respiratory effects of oxygen may be difficult to study specifically but, since pure oxygen cannot be breathed safely for long periods of exercise at very high ambient pressures, the physical effects of oxygen may not be of great practical importance. In this presentation oxygen will be presumed to produce respiratory changes largely by chemical means.

CHEMICAL EFFECTS OF OXYGEN UPON THE LUNGS

Although this presentation is related to respiratory control rather than to pulmonary function, there are several areas of relative ignorance concerning the physiological effects of very high oxygen pressures upon pulmonary ventilation, pulmonary circulation and oxygen uptake which should be mentioned. Prolonged inhalation of oxygen at high pressures is known to result in a toxic pulmonary irritation[5,6] which can proceed to severe chemical damage and death. The question of whether very high oxygen tensions also have direct or indirect physiological effects on the lungs has not been studied. A very high alveolar-arterial

TABLE I

Oxygen and Respiration

	Reference
Effects of altered density and viscosity of oxygen relative to inert gas-oxygen mixtures	4
Effects of oxygen upon chemoreceptor activity	12,14,33,34
Effects of oxygen on CO_2 transport by blood	7,15,16,21,35
Stimulation of respiration by oxygen	13,19,21
Effect of oxygen upon brain circulation	7,22,23a
Depression of respiration at rest by oxygen at high partial pressure	13,27,28,31
Effects of oxygen breathing in exercise	30,31
General effects of prolonged oxygen breathing (increased rate of inert gas removal, atelectasis)	

Po_2 difference observed at high inspired oxygen pressure (3.5 atms) must still be explained by using improved methods of measurement[7,8]. The action of very high oxygen pressures upon bronchiolar smooth muscle and upon pulmonary vessels is not known[9]. While none of these physiological questions is intended to imply that oxygen uptake is limited by oxygen at high pressures, they must be studied to improve our understanding of the over-all effects of hyperoxia.

EFFECTS OF OXYGEN ON CHEMORECEPTOR ACTIVITY

Oxygen reduces the vigorous chemoreceptor activity produced by pre-existing arterial hypoxia[10]. It is also known that in resting, air breathing subjects oxygen administration produces a transient reduction of pulmonary ventilation[11,12]. In our laboratory it has been further found that, at a controlled, elevated alveolar Pco_2, a rapid change from an alveolar Po_2 of approximately 100 mm Hg to an alveolar Po_2 in excess of 600 mm Hg will induce a transient, rapid depression of ventilation with a time lag of about four seconds from the beginning of oxygen inspiration and a time constant of about two breaths (Figure 1)[36]. This effect has in the past been presumed to be chemoreflex and to result from the relief of a "tonic hypoxic drive." While the temporal characteristics of this respiratory effect of oxygen do suggest chemoreflex mediation, a central influence of oxygen must be clearly ruled out. Moreover, even if entirely peripheral it is not adequate to consider that the depression is related only to removal of an hypoxic drive. Since the carotid chemoreceptors respond, not only to hypoxia, but also to changes

in carbon dioxide tension (Figure 2A), it will be necessary to determine whether this initial depression of respiration by oxygen at high partial pressures may, at least in part, be due to a suppression by oxygen of chemoreflex stimulation by carbon dioxide[13]. Figure 2B, derived for this presentation from a study by Hornbein et al[14], suggests that this may indeed be a possibility. Thus, the use of very high oxygen pressures offers a method for studying whether chemoreceptor stimulation by hypoxia and by carbon dioxide are linked via a common mechanism.

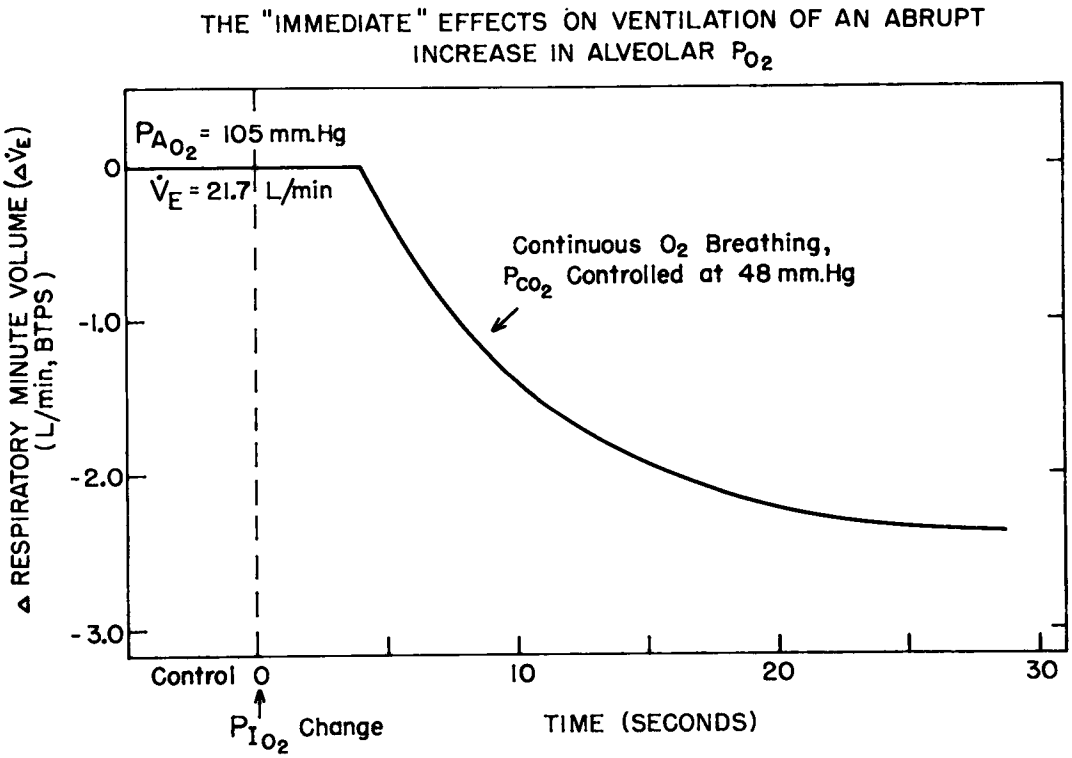

Figure 1. The influence upon respiratory minute volume of an abrupt transition from an alveolar P_{O_2} controlled at 100 mm Hg to the inhalation of oxygen at 1.0 atm (average of six experiments in one subject). Zero time is the time at which the increased P_{O_2} was detectable at the mouth on inhalation. The sudden, sustained administration of O_2 at about 660 mm Hg produced a transient fall in respiratory minute volume from the high level of ventilation associated with an alveolar P_{CO_2} controlled at 48 mm Hg (see text). The effect is more easily quantitated with sustained hyperoxygenation than that effect found with the earlier, one-breath "O_2 test" of Dejours[12]: Ventilation later returns toward the control value, most probably as a result of a slowly developing central accumulation of CO_2. (Unpublished observations. J. J. Downes and C. J. Lambertsen.)

EFFECTS OF OXYGEN ON CO_2 TRANSPORT

We are now well aware that high inspired oxygen pressure, which increases the amount of physically dissolved oxygen in arterial blood, interferes with carbon dioxide transport from the brain by limiting the reduction of oxyhemoglobin[6,7,15,16]. Figure 3 indicates the magnitude of this effect in man when oxygen is breathed at increased ambient pressure, with and without control of arterial Pco_2.

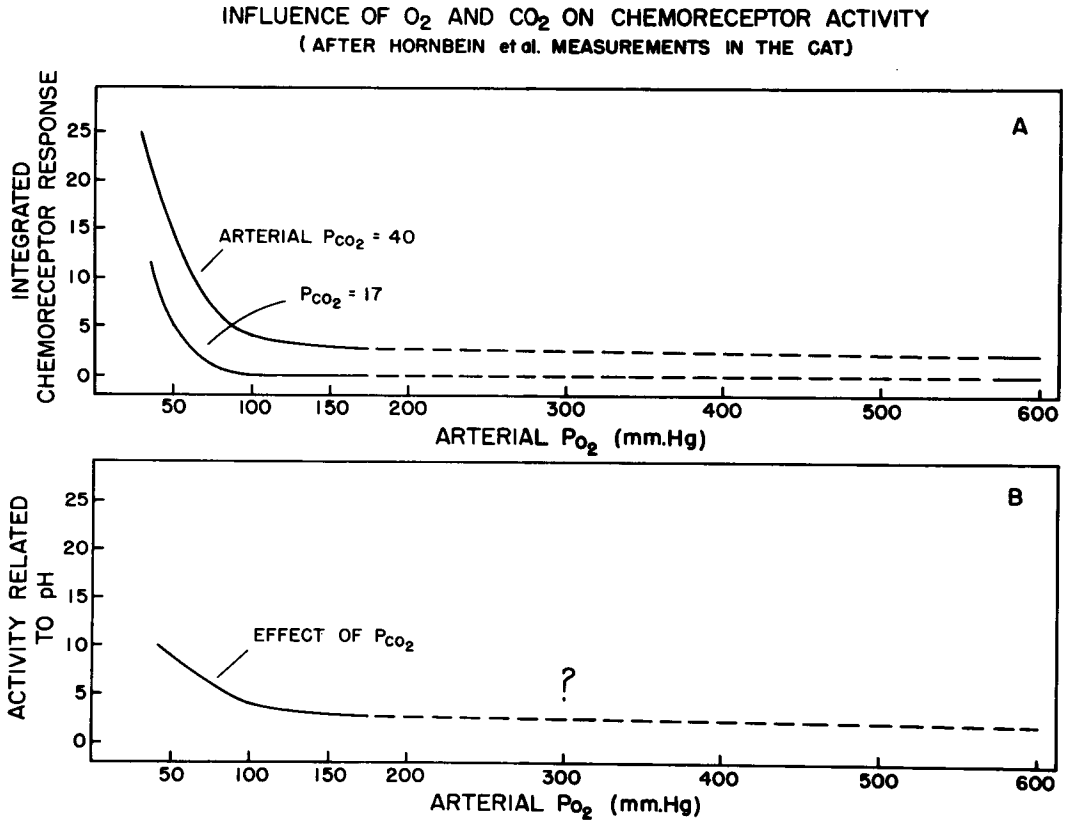

Figure 2. A. Influence of Po_2 and Pco_2 upon electrical activity from the carotid chemoreceptor in a cat (after Hornbein et al)[14]. The diagram indicates that (a) at normal Pco_2, integrated electrical activity in the carotid sinus nerve is affected by lowering or raising arterial Po_2, and (b) at a particular Po_2, altering the Pco_2 will also modify the electrical activity.

B. An effect of Po_2 upon the chemoreflex influence of Pco_2. This diagram, derived from Figure 3A, illustrates the interaction of Po_2 and Pco_2 upon chemoreceptor activity and suggests that, as Po_2 increases, the ability of Pco_2 to stimulate the chemoreceptor mechanism may progressively diminish.

The figure is a pH-bicarbonate diagram with Pco_2 isopleths, descriptive of the Henderson-Hasselbalch equation relating acid-base factors in blood[17]. Arterial and internal jugular venous blood values obtained in a resting control state, breathing air at sea level, are represented by points A_{AIR} and V_{AIR}, respectively[18]. Arterial blood during air breathing (A_{AIR}) has a pH of 7.40, a Pco_2 of about 40 mm Hg and a normal $[HCO_3^-]_p$*. As blood passes through the brain, oxygen is removed, CO_2 is added, pH becomes more acid and Pco_2 rises. This situation, represented by V_{AIR}, is the normal state of brain venous blood.

The normal buffer line of oxyhemoglobin slopes upward to the left from the arterial point obtained during air breathing at sea level[17]. Its slope largely depends upon the hemoglobin concentration; its vertical position depends upon the degree of oxygenation of hemoglobin. It is along this buffer line that CO_2-induced acid-base changes in fully oxygenated arterial blood should occur. Hyperventilation, with the resulting arterial hypocapnia, should cause the arterial point A_{AIR} to move down the buffer slope to the right; administration of CO_2 in air should cause point A_{AIR} to move up the buffer slope to the left. This is different from the situation in which the CO_2 is added to the blood as it passes through the brain and hemoglobin is simultaneously partly deoxygenated. As indicated by Figure 3, the buffer line of brain venous blood is parallel to, but more basic than, that of the more fully oxygenated arterial blood[17]. This parallel shift is related to the release of base which, accompanying deoxygenation of oxyhemoglobin, normally limits the rise in Pco_2 and the increase in acidity of blood in its passage through metabolizing tissues.

The shift in position of the buffer line does not occur when the degree of arterial hyperoxia is sufficient to supply the metabolic needs of a particular organ or tissue entirely from oxygen physically dissolved in the blood. This was nearly the case with the subjects of Figure 3. $V'o_2$ represents the Pco_2 and acidity of internal jugular venous blood in the hyperoxic state. Part of the 5 mm Hg rise in Pco_2 above the air breathing level is due to the cerebral vasoconstriction produced by oxygen breathing; part is the result of the decreased buffer capacity of the now almost completely oxygenated venous hemoglobin (decreased Christiansen-Douglas-Haldane effect)[15]. Point $A'o_2$ represents the acid-base state of arterial blood during O_2 breathing. The lowering of arterial Pco_2 and acidity along the buffer line is probably the result of respiratory stimulation secondary to central hypercapnia[19].

It is possible from these and other empirical data to estimate the central venous Pco_2 which would be obtained if the oxygen-induced fall of arterial Pco_2 were entirely prevented during oxygen breathing. $A''o_2$ represents an hypothetical situation in which oxygen is again administered at 3.5 atms, but in which arterial hypocapnia is prevented by controlling the alveolar Pco_2 at 40 mm Hg. This control can be easily accomplished experimentally[20]. As shown by $V''o_2$ Figure

*The absolute values used for $[HCO_3^-]_p$ in this example do not exacly match those of the original source, since values for pH and Pco_2 are undoubtedly in error by small amounts. For present purposes it was elected to obtain fit in the diagram by minor adjustment of $[HCO_3^-]_p$ values. The relative changes indicated should be quite accurate.

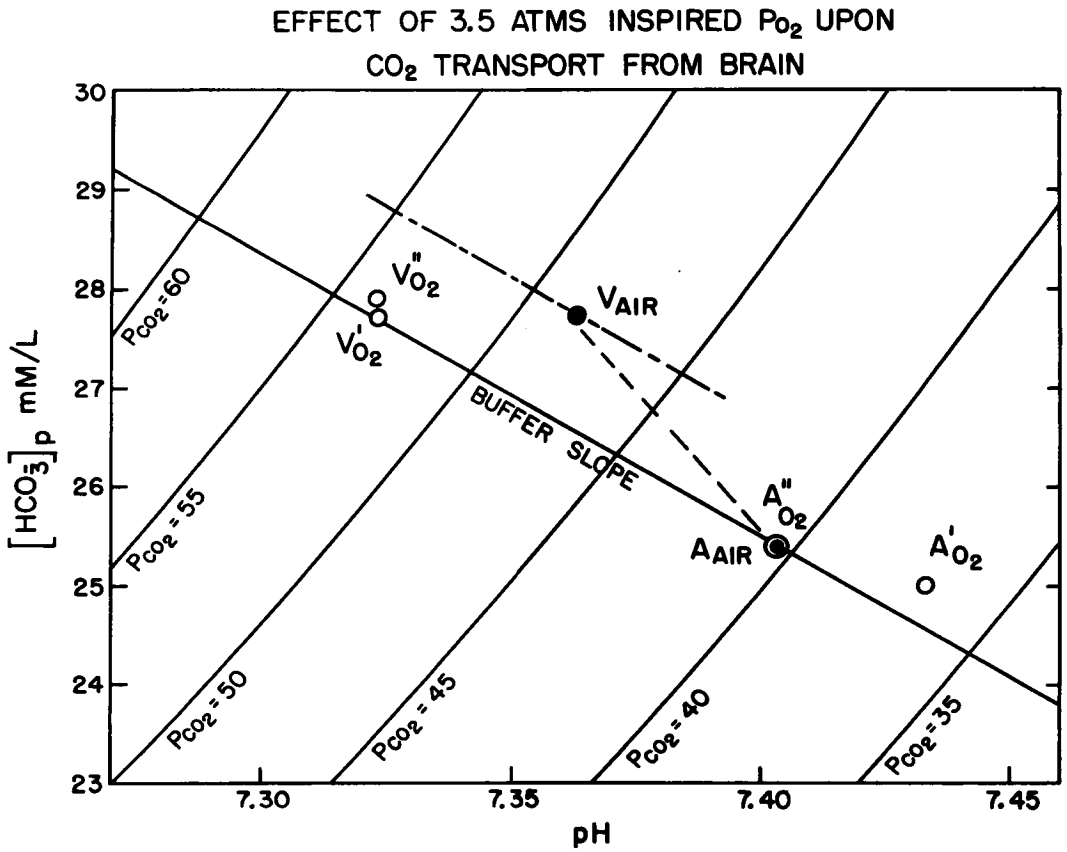

Figure 3. Acid-base paths of blood in its transition from the arterial to the venous state across the human brain (average values in four subjects[18]). See text for details.

3, the central venous P_{CO_2} does not rise further when arterial P_{CO_2} is sustained at its normal level. Abolishing the arterial hypocapnia of point A'_{O_2} restores brain blood flow to normal and, since CMR_{CO_2} remains constant, the amount of CO_2 which enters each milliliter of capillary blood will now be decreased. This effect and that of the increase in the P_{CO_2} of arterial blood entering the brain cancel almost exactly. The result is that central venous P_{CO_2} and acidity remain essentially the same during extreme hyperoxia, whether or not moderate arterial hypocapnia occurs.

The figure thus indicates that, even with complete failure to utilize oxygen from hemoglobin, the maximum rise in central venous P_{CO_2} to be expected with a change from air to oxygen breathing will be about 5 mm Hg both in the free breathing of oxygen and when arterial P_{CO_2} is held at control levels. If higher than normal levels of arterial P_{CO_2} are produced, as by administration of CO_2 in O_2 at 3.5 atm, the internal jugular venous P_{CO_2} will also be increased along the oxyhemoglobin ("arterial") buffer line. The rise of central venous P_{CO_2} will be somewhat less

than the hypercapnia induced in arterial blood, due to the effect of the increasing rate of brain blood flow described previously[19].

EFFECTS OF OXYGEN UPON BRAIN BLOOD FLOW

At the previous symposium considerable attention was given to the effects of high oxygen pressures upon blood flow through the brain[21]. Oxygen administration was then known to produce a distinct cerebral vasoconstriction[7,22]. However, it was questioned whether the reduction of brain blood flow by oxygen was, in fact, due to a direct action of oxygen upon brain vessels or was an indirect effect of the arterial hypocapnia which accompanies the respiratory stimulation by oxygen[7,23a].

Figure 4 shows the well-known cerebral vasoconstriction and lowering of brain blood flow produced by oxygen breathing at one atmosphere[7,22]. It also shows that when oxygen is administered to normal men while holding alveolar P_{CO_2} constant, no detectable cerebral vasoconstriction is produced[23a,24,25]. Thus, it now appears clear that a direct effect of oxygen upon cerebral vessels cannot account for the central CO_2 accumulation and the associated respiratory stimulation which accompanies oxygen inhalation. If there is a direct vasoconstrictor action of oxygen on adult cerebral vessels, it must be minute.

EFFECTS OF OXYGEN ON RESPIRATION

Two effects of oxygen on respiration have already been mentioned. The first, shown in Figure 1, was the production of an abrupt and apparently transient decrease in ventilation. The second effect, a slight respiratory stimulation, occurs when oxygen breathing is continued until a stable state of gas exchange is attained (Figure 5). Figure 5 suggests that this stimulation is related to an increased central venous P_{CO_2}, and that arterial P_{CO_2} is, in turn, lowered by the increased ventilation[19]. Whether the fall in arterial P_{CO_2} limits the respiratory stimulation resulting from this rise in central P_{CO_2} is uncertain, since of the total, powerful respiratory effects of CO_2, even the proportion acting at any location is not yet known[26].

Finally, oxygen can also depress respiration in the stable state[13,27,28,29]. Figure 6 shows that oxygen administered at 2.0 atmospheres decreases the slope of the ventilatory response of normal men to the administration of carbon dioxide. When, as in Figure 6, measurements of pulmonary ventilation are plotted against end-tidal P_{CO_2} values in the conventional P_{CO_2}-ventilation response curve, the oxygen breathing curve actually crosses the air breathing control curve. Thus, from this diagram alone an unlikely combination of effects is suggested, i.e., that high oxygen pressures stimulate breathing at low levels of alveolar P_{CO_2}, do not alter ventilation at moderate P_{CO_2} levels (45-50 mm Hg), and depress ventilation at higher P_{CO_2} levels. Clearly, more information is needed.

In Figure 7 the respiratory effects of oxygen inhalation at 1.0 atm are related not only to the arterial but also to the venous side of the brain circulation; this provides an opportunity to differentiate between the apparently conflicting respiratory effects of oxygen shown in Figure 6. In the P_{CO_2}- ventilation response curves obtained by referring ventilation to changes in central venous P_{CO_2}, oxygen

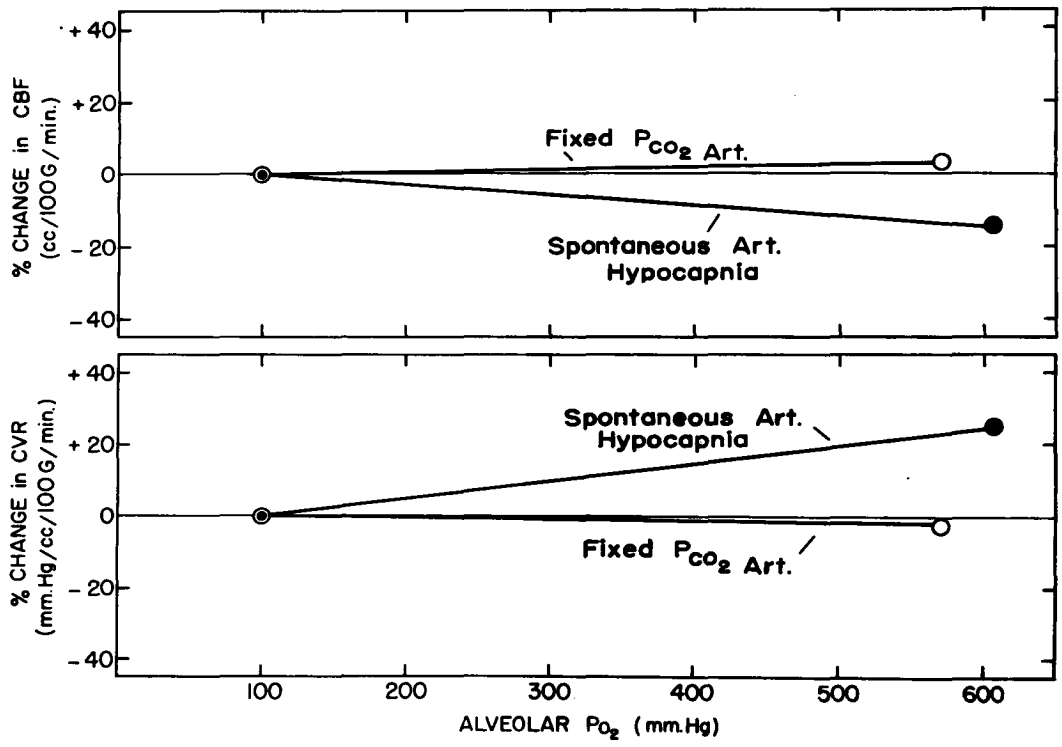

Figure 4. Effects of oxygen administration on cerebral blood flow and cerebral vascular resistance (average values in six and eight subjects[2,7]). Solid circles, ●, are measurements made when the usual, spontaneous lowering of alveolar P_{CO_2} occurs; open circles, O, indicate alveolar P_{CO_2} maintained at the air breathing control level. The cerebral vasoconstrictor effect of oxygen breathing is seen to occur only when hypocapnia is allowed to develop[23a].

is seen to have caused only depression of the ventilatory response to CO_2, regardless of the level of P_{CO_2} imposed. It therefore appears that oxygen administration, either in the changing or in the stable state, does not stimulate at one level of P_{CO_2} and depress at another, but simultaneously stimulates and depresses respiration. The increase in respiration appears related to a rise in the level of a central, P_{CO_2}-related stimulus and is probably partly counter-balanced by a central or peripheral chemoreflex effect of arterial hypocapnia. The depressant effect of oxygen also limits the stimulation resulting from increased central P_{CO_2}. Even in the transient state illustrated by Figure 1, ventilation probably returns toward control levels as central accumulation of CO_2 introduces an indirect, opposing stimulant mechanism while the depressant mechanism persists.

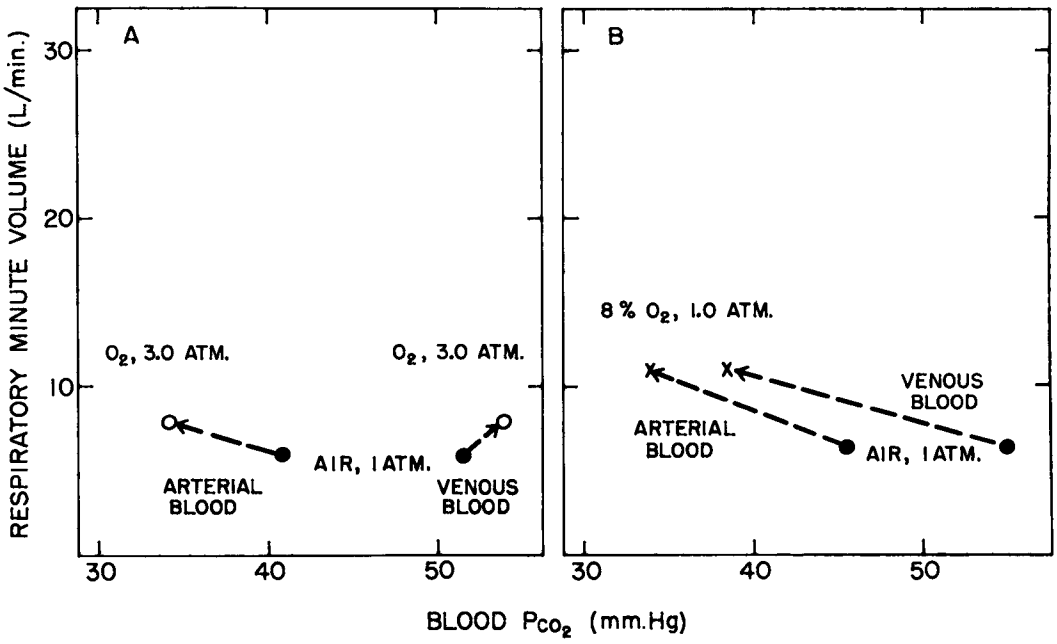

Figure 5. Effects of high and low inspired Po_2 upon relationships of respiration to the acid-base state of arterial and internal jugular venous blood (average results in eight and six normal men[19]). Both high and low inspired Po_2 lead to increased ventilation and to a consequent arterial hypocapnia which should limit the degree of hyperventilation. While the relationships of ventilation and arterial Pco_2 are similar in hypoxia and hyperoxia, the relationships of brain venous blood Pco_2 and respiration are grossly dissimilar in these different states of oxygenation. The figure shows the central hypercapnia of oxygen breathing[19] and the exaggerated central hypocapnia of anoxia[23c]. In each instance the effect upon central Pco_2 is brought about in part by lowered arterial Pco_2 and in part by change in brain blood flow.

THE MAXIMUM DEPRESSION OF RESPIRATION WITH OXYGEN ADMINISTRATION

Both the stimulation and the depression resulting from oxygen administration appear greater at 2.0 atm than at 1.0 atm of inspired oxygen. An important question concerns the maximum magnitudes of these actions of oxygen. When inspired Po_2 is increased and arterial Pco_2 is held constant at a normal level, central CO_2 elevation and its effect on respiration should reach a limit at an inspired Po_2 of 3.5 atm or less. It is not yet certain whether the O_2-induced depression of the ventilatory response to CO_2 is self-limited or whether, as Po_2 is raised, it will continue to increase until complete abolition of respiratory stimulation by CO_2 occurs. Figure 8 shows a preliminary investigation of this question. Repeated measurements on one man of the respiratory reactivity to changes in Pco_2 at 0.2, 1.0, 2.0 and 3.0 atm inspired Po_2 suggest that the effect of oxygen increases, at least to two or three atmospheres. More experimental

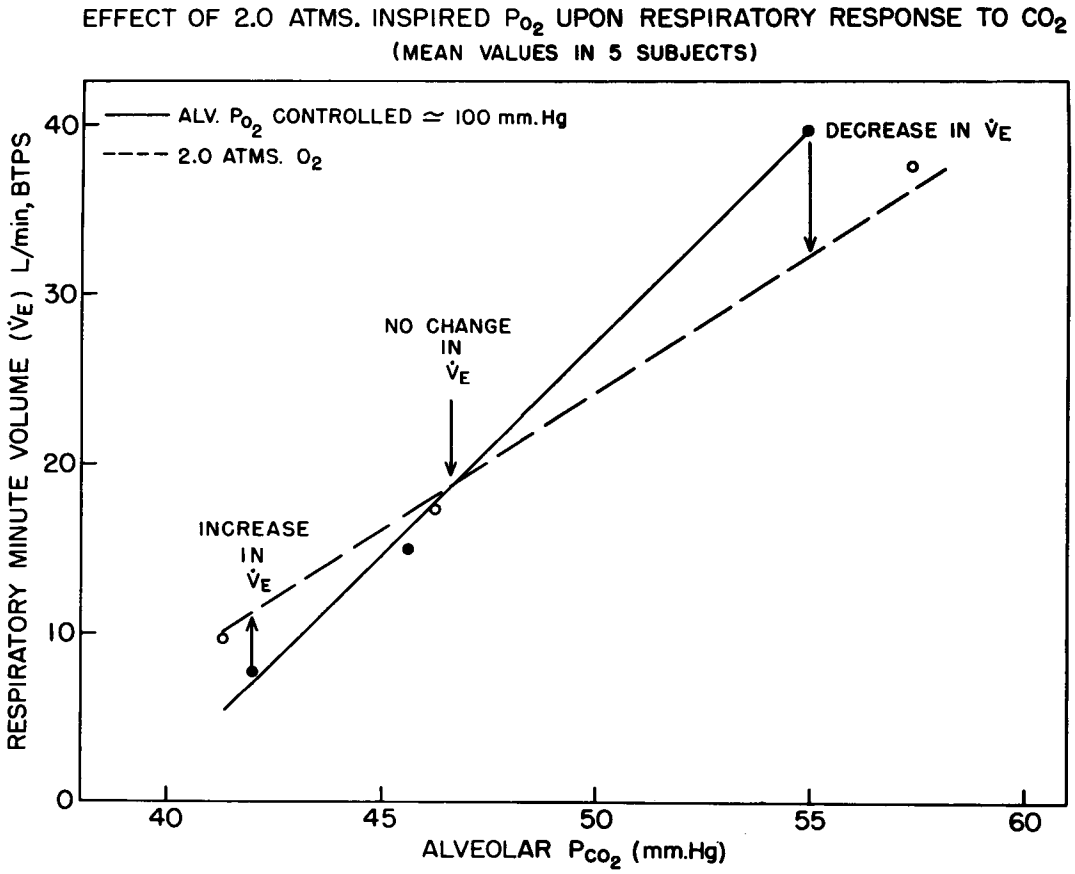

Figure 6. The respiratory response of normal men to elevated P_{CO_2} at 2.0 atmospheres ambient pressure (average values in five normal men. The data of this figure is distinct from but confirms the preliminary study previously reported[13]). This figure shows that oxygen produces a gross decrease in the respiratory reactivity to CO_2. The actual increase in ventilation at low alveolar P_{CO_2}, together with decrease in ventilation at high P_{CO_2}, produces a distinctive crossing of CO_2 sensitivity curves not previously seen with any known agent[13].

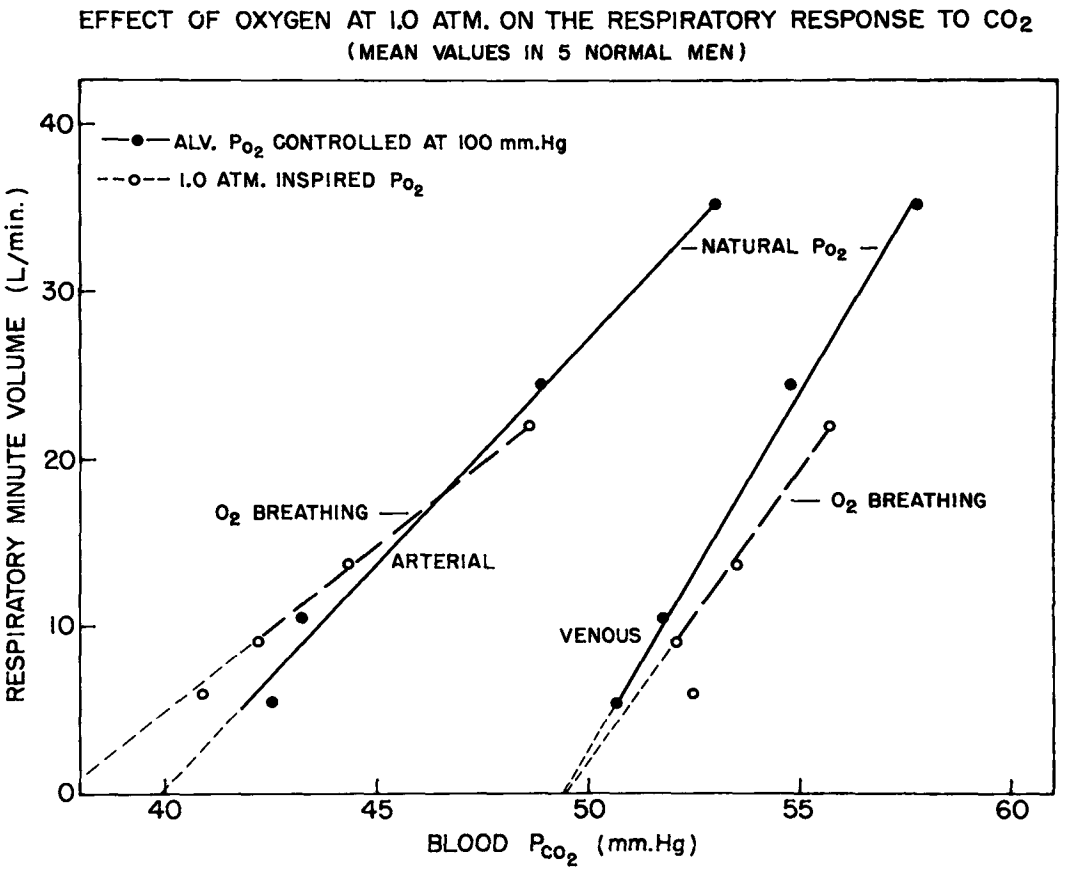

Figure 7. Influence of oxygen inhalation at 1.0 atm upon the relation of respiration to the P_{CO_2} of arterial and internal jugular venous blood (average values in five normal men). The solid and dashed lines are regression lines. The data for the condition of oxygen breathing without added CO_2 were omitted in deriving the regression of ventilation on P_{CO_2} during oxygen breathing; this was done to avoid introducing the uncertain influences of subnormal arterial P_{CO_2} as variables in this study. A peculiar crossing of the P_{CO_2}-respiratory response curves occurs, but only when respiration is related to arterial P_{CO_2}. When brain venous P_{CO_2} is used as the reference for determining respiratory response curves, the oxygen breathing curve is seen to be depressed below that for air breathing at all levels of P_{CO_2}[13]. No paradoxical crossing of the venous CO_2 response curves occurs.

evidence must be obtained at 3.0 atm to determine whether the O_2 effect has reached a maximum at 2 to 3 atmospheres ambient pressure or whether it progresses as inspired Po_2 is raised still further. One obvious, practical difficulty in obtaining such data is that to study effects of oxygen upon respiratory response to CO_2, carbon dioxide must be administered with the oxygen; and CO_2 is known to accelerate the development of the central nervous system form of oxygen toxicity.

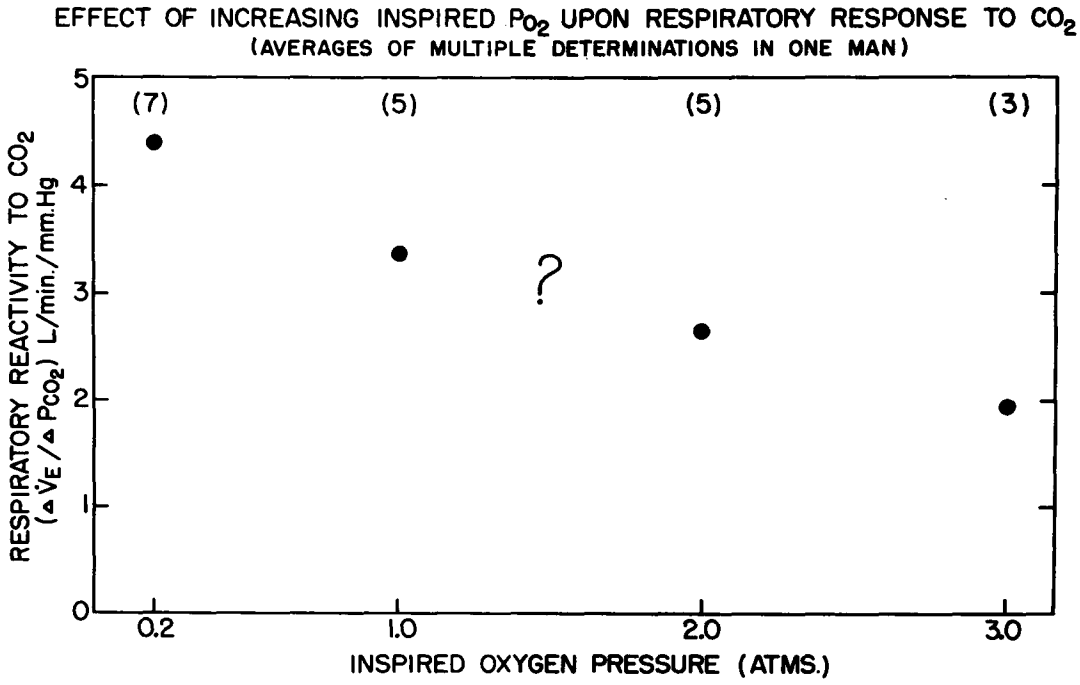

Figure 8. Magnitude of the depression of respiration by oxygen at high partial pressures (average values in one man). Except for one study at 0.2 atm and one at 1.0 atm, all measurements were obtained at 3.0 atmospheres ambient pressure. The CO_2 response curves for 0.2 atm inspired Po_2 were determined with alveolar Po_2 controlled at 100 mm Hg. The effect of O_2 at 2.0 atms inspired Po_2 is greater than the effect at 1.0 atm, but no curve has been drawn since there is not yet sufficient data to determine whether the influence of an inspired Po_2 of 3.0 atmospheres is greater than that of 2.0 atmospheres.

EFFECTS OF HIGH INSPIRED OXYGEN PRESSURES UPON THE HYPERPNEA OF EXERCISE

Even at 1.0 atmosphere, oxygen breathing reduces the degree of exercise hyperventilation[30]. Studies at 2.0 atms of inspired O_2 have shown a clear correlation between the degree of respiratory depression by oxygen in exercise and the ability of oxygen to limit the degree of acidemia produced by fixed acid spillover from the exercising muscles[31]. However, it remains possible that

this may represent only part of a complex effect of oxygen in exercise, since Asmussen and Nielsen have shown that the fall in ventilation during exercise when O_2 is abruptly administered occurs more rapidly than does the fall in circulating blood lactate[30]. These astute workers long ago suggested that increased P_{O_2} removed an unidentifiable chemoreceptor stimulant[30]. It is quite possible that the effect postulated for oxygen by Asmussen and Nielsen is not the removal of a peculiar respiratory stimulant, but is the same depression of the respiratory response to acidemia which has not been found to be produced when O_2 is substituted for air in CO_2 breathing (Figures 6 and 7).

Figure 9 shows the effect upon ventilation of 0.2 and 2.0 atms of inspired O_2 at various degrees of muscular exercise[31]. At moderate work rates oxygen breathing reduces total ventilation less than 20 per cent. The figure also indicates the relationship found by Dejours[32,23b] to describe the abrupt "neurogenic" change in ventilation on ceasing exercise at various work loads. If the difference between this regression line and the line for ventilation breathing air represents the sum of all chemical and metabolic factors of respiratory control in exercise, oxygen is seen to reduce this component of the stimulation by about 30 per cent. This gross reduction in ventilation may in fact be a composite of the two depressant effects cited (i.e., relief of muscle anaerobiosis and decrease in the ventilatory response to acidemia), countered in part by the same elevation of central P_{CO_2} and $[H^+]$ that is found when oxygen is administered at rest[31].

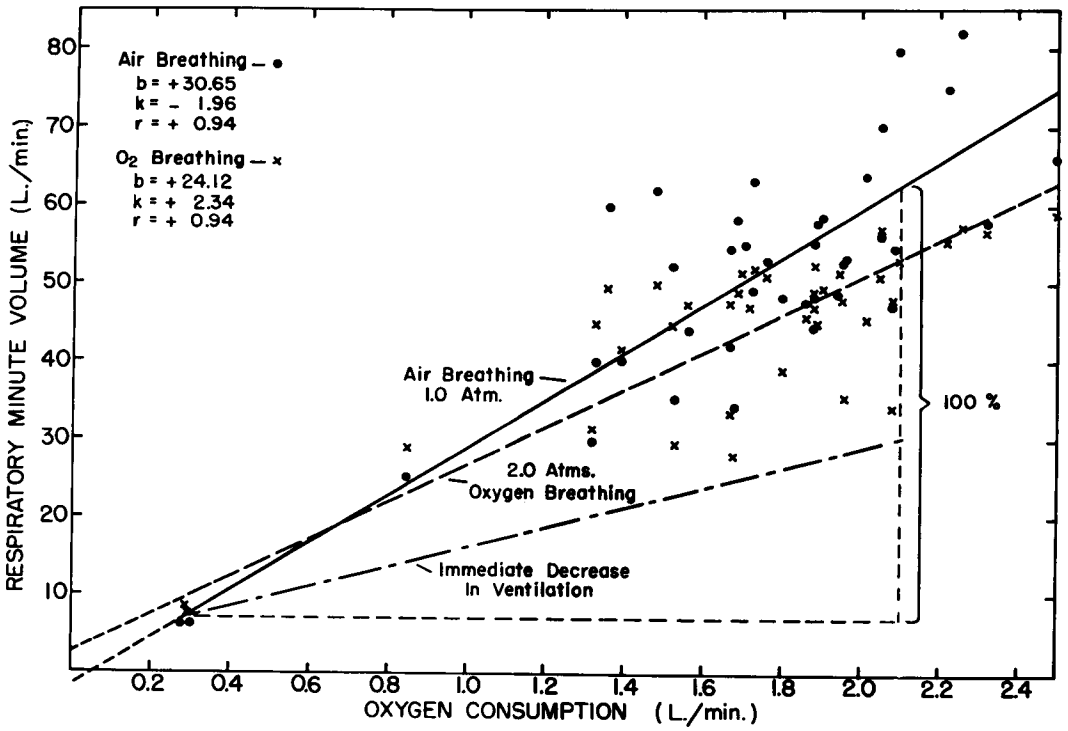

Figure 9. Influence of oxygen upon respiration in exercise (after Lambertsen et al[31]). The regression of ventilation on metabolic rate in exercise, breathing air, is described by the upper solid line. As shown by the middle line, oxygen breathing at 2.0 atm reduces the slope of the regression line. This effect is probably caused in part by diminishing anaerobic metabolism and fixed acid production, but is possibly due in part to mechanisms related to the same type of depression of the respiratory reactivity to CO_2 acidemia which has now been demonstrated at rest. To aid in estimating the degree of the O_2 effect upon the acidemia of exercise, uncomplicated by neurogenic influences upon exercise hyperventilation, the figure has been drawn to include, as a third line, the regression on work load[32] or metabolism[23b] of the abrupt fall in ventilation which occurs as work ceases[34]. It can be seen that the respiratory depression by oxygen in moderate exercise, which is only about 20 per cent of the total ventilation, is actually as great as 30 per cent of the ventilation ascribable to the sum of chemical factors.

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FOURTH SESSION
EFFECTS OF OXYGEN IN DIVING

J. Bean, Chairman

FILM

OXYGEN CONVULSION IN MAN
Narrated by C. J. Lambertsen

The film shows one of a series of schizophrenic patients who was under a trial of therapy with oxygen convulsions in our laboratories. The exposure was of 2 per cent CO_2 in 98 per cent oxygen at 4 atmospheres pressure. You will note that the exposure to the gas has been on for 15 minutes by this time. The subject is hyperventilating but not violently with the 2 per cent CO_2 at 4 atmospheres. This partial pressure is equivalent to 8 per cent CO_2 at sea level. The moderate degree of response to CO_2 recalls the depressant effect of oxygen. Notice the twitchings of muscles about the eye. The patient raises his hand on request. I mention this to point out that in oxygen toxicity consciousness is retained right up to the moment of the development of a convulsion. As the convulsion begins there is an arching of the back, stiffening of the arms, and then a fairly typical epileptic form of convulsion. There is reddening of the skin, the result of peripheral dilatation with hyperoxygenation of the blood. It took about 20 minutes to precipitate this convulsion. The CO_2 was added in order to shorten the oxygen exposure required. On previous days this subject had had about six oxygen convulsions. Appropriate neurological examination and cerebral spinal fluid and blood chemistry studies gave no indication of harm from the actual episodes of oxygen toxicity. You must keep in mind that underwater it is an entirely different matter from the laboratory study, since drowning or failure of rescue is likely. Recovery from the convulsion is usually quite prompt; the subject may not remember having gone into convulsions but may remember some of the preliminary symptoms.

DISCUSSION

BEAN: Dr. Thomas, what is the relationship of your findings concerning brain metabolism to the influence of blood glucose? Years ago we found that there was an increase in blood glucose in O_2 poisoning which was probably due to activity of the sympathetics. We injected glucose intraperitoneally to elevate the blood glucose. It offered some protection against oxygen. On the other hand, there are also some phases where you have a decrease in glucose.

THOMAS: I mentioned that one cannot account for oxygen consumption as coming directly from glucose. Nevertheless, glucose accounts directly or indirectly for the maintenance of normal cerebral function. A blockage of glucose metabolism by reducing blood glucose level with insulin, by removing the liver, or by adding a metabolic competitor like desoxyglucose, will produce convulsions. Now, if the glucose level was grossly elevated, it might be possible to overcome that block. I do not believe that glycolysis can maintain normal cerebral function, although according to Geiger one can maintain a convulsion on

substrates other than glucose. Geiger perfused the brain of a cat and found that, at the resting level of oxygen consumption, about 30 per cent of the CO_2 produced came from glucose. When he added pentylenetetrazol to precipitate the convulsion, oxygen consumption rose and the rate of glucose utilization went way down. However, all the glucose utilized was accounted for by lactic acid production. He also showed in this experiment that all of the extra oxygen consumed came from phospholipid and protein. This is distinctly an abnormal situation, but I believe it could happen in oxygen toxicity.

LAMBERTSEN: You mean after the actual convulsive expression of oxygen toxicity begins? This is not synonymous with the beginning of oxygen toxicity.

THOMAS: Yes, after the convulsion begins. Then you may not be operating so much on glucose, but the extra metabolism does not have to be from glucose.

LAMBERTSEN: Does this have to bear any relation to the etiology of the oxygen toxicity though? Or does it relate primarily to the chemical events during the actual electrical spread and convulsions?

THOMAS: This relates to the actual convulsion. The problem with convulsive behavior is that we can now describe fairly well what happens during convulsions, both electrically and chemically, but cannot really say what starts a convulsion. We do know that if you interfere with the energy metabolism you can produce something like this.

LAMBERTSEN: I would like to challenge a statement by Dr. Thomas that the brain was well known to be the most susceptible tissue to oxygen toxicity. This needs discussion, since it bears upon the difference between actual toxicity and the pattern of expression of the toxicity. We have clear indices of central nervous system toxicity in that twitches or convulsions occur. We therefore know when the brain is poisoned. We do not know if toxic effects on the leg or liver have occurred prior to the development of convulsions. Did you really mean that the brain is more susceptible than, for example, the lung?

HAUGAARD: There are distinct differences from one tissue to another in vitro but they are not very large. I will not say that the brain is very much more sensitive than other tissues. We have found very definite inhibition of metabolism by oxygen in heart homogenates. There is not a great deal of difference between the heart homogenate and the brain homogenate, so I think it is an important point that Dr. Lambertsen has brought out, that the effects of the derangement of the metabolism are different in different tissues. I think that was the point he wanted to make. The derangement in carbohydrate metabolism in the brain undoubtedly would have effects on the norepinephrine, the histamine and the acetylcholine that exists in the brain.

THOMAS: According to the report that you made with Stadie and Riggs, as well as those by Dickens, it was felt that brain was more susceptible.

HAUGAARD: We did studies with heart homogenates in which we studied the effect of 100 per cent oxygen on carbohydrate metabolism and found that 100 per cent oxygen when compared to air or 7.4 per cent oxygen definitely decreased metabolism. The findings are very much in line with those of Dr. Thomas, although we used much simpler techniques and did not go as far in trying to find the mechanism of action. We did study the effect of a chelating agent, EDTA (ethylenediamine tetra-acetic acid), and found that when we added this chelating agent in a very small concentration, about 10^{-5} molar, all the toxic effects of oxygen disappeared. We could also increase the effects of oxygen by adding tiny amounts of copper ions. So, in this in vitro system, trace metals seemed to play a part. The question, of course, is how much the in vitro system describes what really happens in the intact animal. Gerschman has also found that some metal chelating agents afford some protection against oxygen poisoning in the intact animal.

LAMBERTSEN: Your studies were at sea level, were they not?

HAUGAARD: All of my own recent experiments are carried out at sea level pressures.

BECKER: I would just like to say, relative to the discussion of glucose, that it was shown in the thirties that the infusion of glucose would significantly protect against anoxia and presumably it might protect against any hyperoxic barriers that were set up.

LAMBERTSEN: Do you know whether hypoglycemia potentiates oxygen toxicity?

BEAN: Certainly insulin does. It may have some other than hypoglycemic effects but it has a very distinct potentiating influence on oxygen toxicity, not only on the convulsive seizure but also on the pulmonary effects of oxygen.

THOMAS: That is very interesting because most people do not believe that insulin potentiates glucose metabolism of the brain.

SCHAEFER: Dr. Lambertsen presented a slide showing the effect of oxygen upon the respiratory response to CO_2. The reactivity declined with increasing oxygen pressure. Cunningham and Lloyd have shown that the effect of oxygen in CO_2 response is small and reaches a limit at less than one atmosphere of O_2[1]. Did you see any change in the threshold to CO_2?

LAMBERTSEN: Dr. Schaefer, actually one of the reasons for doing these particular studies was our earlier observation that oxygen had a gross effect upon the respiratory response to CO_2, which was not fully expressed even at 2.0 atm. We wish to learn at what tension the maximum effect of oxygen on CO_2 sensitivity occurs. We know that it is not at the low Po_2 that Cunningham et al interpreted it to be, since the method used by them was aimed at relief of anoxia and was not valid for study of a specific oxygen effect[2]. The only interpretation we can give to our present measurements at increased ambient pressure is that as you increase the oxygen tension there is definitely a prominent decrease in CO_2 reactivity. We do not know whether, even at 3.0 atmospheres, we have found the

limit of this new effect of oxygen. We do not yet know the shape of the curve of the oxygen effect.

NEPTUNE: I would like to ask Dr. Becker if we should defer further studies of lipid peroxides because of the difficulty in measuring them accurately, and should wait for a better method. I am thinking particularly of the thiobarbituric acid method of measurement. Many retractions in the literature concern studies of lipid peroxides.

BECKER: The method is difficult, though we found a way to improve it by freeze thawing the homogenate before running the tests. This gave us mugh higher blanks. However, I am pessimistic about determination on whole brain. The method is good enough so that if something were happening in a diffuse way we would have been able to pick it up. Until some good micromethod is developed for measurements of tissue, slices of cortex, hippocampus and thalamus I am not willing to drop the work as yet.

BEHNKE: In the in vitro study of brain tissue, it is important to designate where the tissue is taken and it would be interesting to take tissue that is sensitive, viz., respiratory tissue. The visual cell system is especially sensitive and it would be extremely interesting to study this tissue.

With reference to in vitro work we know that the oxygen tension in vitro is much higher than it is for the same ambient pressure in vivo, as Dr. Lambertsen and others have shown. In in vitro systems can you add anzymes that will bring about a reversal of toxicity? What is the effect of hypothermia in vitro? What is the effect of adding CO_2? Finally, tell us in biochemical terms why the convulsive seizures stop.

THOMAS: During a convulsion the patient does not breath. Thus, I should think that the oxygen tension in the brain should go down rather markedly.

LAMBERTSEN: This is true for convulsions during air breathing at sea level, but not for oxygen breathing. Brain oxygenation should skyrocket during breath-holding on oxygen, due to the rise in arterial P_{CO_2} which accompanies simultaneously decreased ventilation and muscular exercise of convulsions. So I believe a subject convulsing at high oxygen pressures would be poisoned more and more during the convulsions in spite of increased central demand for oxygen.

BEAN: Dr. Wittner, would you like to comment on your work with SH groups?

WITTNER: The work with SH groups in paramecium has shown that glutathione, coenzyme A, cysteine and BAL would protect against oxygen toxicity for short periods of time up to seven atmospheres absolute. We also found that magnesium and cobalt in dilute concentrations (10^{-5} M), along with pyruvate were remarkably effective in protecting against oxygen toxicity. I think that pyruvate and divalent cations have also repeatedly demonstrated protection.

GILBERT: It has been the feeling of some investigators that the thiobarbituric acid (TBA) test is a test, not for peroxide but, maybe even more important, for the antioxidant defense in the system. This test may be pertinent to the discussion of oxygen toxicity, even though it does not actually test for a peroxide. Concerning the antioxidants, one should be cautioned against thinking that antioxidants do not always counteract the effects of oxygen. We have demonstrated that glutathione can act as a pro-oxidant. This is not surprising providing that one does not believe in a free radical mechanism of oxygen toxicity as postulated by Gerschman and coworkers. It is possible that oxygen can be activated by some type of hydrogen donor, like glutathione acting as a pro-oxidant. It is possible that it can act as an antioxidant by removal of free radicals. Depending upon the circumstances in your system, it is going to be very difficult to determine whether something will be an antioxidant or a pro-oxidant. Glutathione does not appear to have a protective effect at lower pressures of oxygen but it does at higher pressures of oxygen. We have also learned that at one atmosphere cobalt does seem to have a very pronounced but small protective effect against oxygen toxicity in paramecia. The fact that the antioxidants can act as pro-oxidants is extremely well known. I can also report some in vitro experiments which we did some years ago on the effects of glutathione oxidation on exposure of it to high oxygen tensions. We exposed glutathione to about 140 atmospheres of oxygen pressure and added some EDTA. This practically inhibited the oxidative substance for about 100 days.

Concerning the effects of high pressure oxygen on functioning tissue I would like to mention some experiments recently done on the membrane potential of muscle cells exposed to high oxygen tension. We have found that, with isolated frog sartorius muscle exposed to 140 atmospheres of oxygen, the membrane potential is not altered immediately after the oxygen exposure but that two hours after removal from oxygen there seemed to be a decrease in the membrane potential. Glutathione did seem to protect against this inhibition of the depolarization of the membrane.

BECKER: What is the actual oxygen tension in the brain of the intact animal during oxygen toxicity? On the basis of my pathological observations on tissue, I wonder whether the brain really isn't anoxic, at least in experimental animals.

BEAN: Certainly in the intact animal where you have lung damage, the death I am sure is due to anoxia. At the cellular level you might refer to effects of high oxygen pressures as a hyperoxic anoxia. One of the complicating features of oxygen toxicity is that of deciding just where oxygen is involved. Is it poisoning by oxygen? Perhaps it is not. Perhaps it is CO_2. Perhaps it is low oxygen. Perhaps it is something else entirely.

LAMBERTSEN: Dr. Bean, I think that what Dr. Becker is getting at is that he thought there was a very great possibility in some of his experimental animals exposed to high oxygen pressures, that the animals were actually anoxic, excepting at the lung-air interface. This occurs, and the systemic anoxia due to pulmonary damage by high oxygen pressures is one of the most serious limiting factors in the study of oxygen tolerance in intact animals. Systemic hyperoxia may not exist even while the animals are dying of pulmonary hyperoxia.

BROWN: Has anyone an actual determination of mitochondrial reduced pyridene nucleotides at high oxygen pressures?

THOMAS: Chance has studied these in the kidney or the brain but he has not gone above about 2 atmospheres pressure. Activation of the system to excite DPNH requires about seven or eight hundred volts in a hot circuit which complicates work under hyperbaric conditions.

BEAN: Dr. Becker, did you imply that there was a specific kind of effect on the mitochondria?

BECKER: I want to leave the impression that none of these changes that I have demonstrated with oxygen are particularly unique to oxygen toxicity. They have been seen in other necrobiotic processes. The only effect we found that seems rather unique was the loss of polyphosphatase activity in the blood vessels of the lung. This itself is not unique either because you see it in zones of pneumonitis. But I have not seen it when animals breathed ether or chlorine. We only had two animals and they died rather quickly. This may come close to a specific effect of oxygen on the capillary membrane. This effect was not seen in the brain. Histochemical methods are not quantitative. Quantitation depends upon biochemical determination.

NEPTUNE: I would like to comment on Captain Behnke's question of why convulsions cease. We should point out that in Thomas' metabolic work, only one pathway was studied. There are alternate pathways for carbohydrate metabolism. It is very possible that equilibria could be established in which alternate pathways were involved. This may conceivably offer a biochemical explanation for termination of convulsions.

WORKMAN: We are certainly anxious to understand perhaps why the oxygen convulsion stops. However, it is important to recognize that in a number of cases, even upon return to air breathing, the convulsion tends to continue and eventually has to be terminated with barbiturates. Convulsions are therefore not an all or none phenomenon.

BEAN: Dr. Lambertsen, would you comment on Dr. Behnke's question?

LAMBERTSEN: Too many investigators tend to consider "oxygen poisoning" and "oxygen convulsions" to be the same thing. The convulsion is an incident in the sequence of events which comprise oxygen toxicity. This has been demonstrated in some of our own studies in which a patient who continues the breathing of oxygen after going through an oxygen convulsion, tends to return to consciousness before having another convulsion. Therefore, the convulsion is not the end point of oxygen toxicity. It is an event triggered in the central nervous system in the course of the prolonged period of developing toxicity.

BEAN: Would you comment further on the effect of high oxygen pressures on the capillaries in the brain?

BECKER: I could see no effect of oxygen on the brain capillaries. The only vascular changes I could see in capillaries were in those of the lungs. This

had made me wonder if the brain in these experimental intact animals was actually anoxic, rather than hyperoxic due to pulmonary damage. You know these small animals exposed to high oxygen pressures are quite pink for a while and then become very pale, but this could be a peripheral vasoconstriction. None of them stay pink for very long in high pressure oxygen.

BEAN: Some of the Swedish workers have demonstrated quite convincingly that there are changes in the cerebral vessels, particularly of young mice exposed to very high Po_2 for prolonged periods of time. This may relate to the phenomenon of retrolental fibroplasia changes which also have been induced in younger animals such as mice.

ROSENBAUM: When animals are used for studies of early pulmonary irritation, the method of killing the animals and removing the lungs affects the results. How were the animals in Dr. Becker's studies killed?

BECKER: We are aware of this problem. When normal animals are killed under nembutal anesthesia, the lungs look relatively normal. When animals are killed by crushing the cervical thoracic spinal cord and the chest is immediately opened to remove the lungs there are no abnormal findings. However if an animal is allowed to thrash about for five minutes there are focal areas of acute red cell exudation, some pulmonary edema, and acute hemorrhage into the lungs. Most of our animals were therefore killed either under nembutal anesthesia or the cervical thoracic spinal cord was crushed and the lungs were removed immediately.

BEAN: We should now turn attention to discussion of the paper by Dr. Pegg.

MACKAY (S): If man were to be exposed to the "breathing" of an aqueous solution, would an artificial oxygenator of his blood be necessary to cover the period of removal of the fluid from his lungs?

PEGG: In suctioning out the lungs of dogs, it would seem that you can return the lungs to normal function. We had thought that possibly the last breath of solution should be very hypotonic and it would then be absorbed more rapidly. However, we have not tried this.

LAMBERTSEN: Dr. Pegg, I thought I heard you say that one of the reasons for your interest in breathing oxygenated fluids at very high Po_2 was that oxygen toxicity is thereby prevented. What makes you think that this would be the case? Isn't it true that the lungs will be exposed to a high oxygen pressure and thereupon be poisoned by the high oxygen tension in the fluid, even though the arterial blood is not excessively oxygenated? In addition the gross acidosis due to inadequate CO_2 presents another form of gas toxicity.

PEGG: No. Presumably the lungs would not be exposed to any greater oxygen tension at the alveolar lining than they would if the breathing medium were gaseous. Otherwise this would be reflected by an increased Po_2 in the arterial blood.

LAMBERTSEN: Do you feel then that when aqueous fluids are breathed the arterial Po_2 is really a reflection of the alveolar fluid Po_2? This would imply no added diffusion barrier. I believe that you are dealing with a complex system in which the linings of the bronchioles and larger passages of the lungs, where gas exchange is minimal, would be exposed to extremely high tensions of oxygen with which the fluid is artifically equilibrated. This suggests that one of the reasons for failure of survival, even after removal of fluids, is oxygen poisoning of the lungs. In this case, removal of fluid is not the only problem in survival. Do you have some thoughts on this?

PEGG: Certainly the passages within the lungs that don't exchange gas as rapidly as the alveoli do would be exposed to higher oxygen tension. The alveolar membranes themselves should not be hyperoxic, because of the diffusion of oxygen across the alveolar membrane, which would have the same thickness as normal. Diffusion would be from the outer shell of liquid within the alveolus.

BEAN: Did you see convulsions at anytime in any animals exposed under these conditions?

PEGG: No, we did not. However, when we brought rats back to the surface after brief exposure to 20 atmospheres and autopsied them immediately, there were bubbles in the arterial and venous blood. This is compatible with the foaming that we saw when we drew arterial blood samples from the same animals.

BEAN: Dr. Lambertsen, do you have any comments on this? Why was there a postponement of the convulsive seizure when the animal is breathing in a high oxygen tension water solution?

LAMBERTSEN: I hinted at that by pointing out that the arterial oxygenation is still not very high and I was trying to call attention to separate central and pulmonary oxygen toxicity. If the arterial oxygen tension is not high, then brain oxygenation is not going to be high. I was anxious that we not miss the point that there is nevertheless a high Po_2 in the lungs, required for even minimal arterial oxygenation, and that this deserves careful appraisal before it is dismissed as a source of pulmonary oxygen toxicity. At fluid oxygen tensions too low to produce pulmonary toxicity, arterial oxygenation will be inadequate to support life.

MACKAY (S): How fast would pulmonary surface active material be expected to generate itself after having your lungs thoroughly washed out?

PEGG: Dr. Clement's guess, when I asked him, was that if the lung was functioning normally it would regenerate within 24 hours. It is interesting to note that hyaline membrane babies go for about three days in respiratory distress. If they survive the first three days they usually live. Do you think that the hyaline membrane found in water breathing animals is the same change that you find in actual human hyaline membrane disease?

PEGG: Our evidence indicates that it is the same material; the positive PAS stain is the same.

BEAN: It is usually denied that oxygen affects the hyaline membrane in the human baby.

PEGG: I can add this. It is known that excessive exposure to oxygen, for a minimum of 48 to 72 hours, will itself produce hyaline membranes in rats. In order to control this factor in our studies we tracheostomized a rat under ether anesthesia and placed him in the continuous positive pressure apparatus. He died within 12 hours but did not have hyaline membranes in the lungs. They were just grossly overinflated from the positive pressure.

BECKER: "Hyaline membrane disease" in infants occurs before any oxygen therapy is given. Whether there actually are hyaline membranes present prior to oxygen administration is not certain, because the infants are treated with oxygen and then they come to autopsy where hyaline membranes are found. No one has done a great deal on the chemistry of hyaline membranes; the fact that they are PAS positive doesn't mean much since all fibrinoid material is PAS positive. These hyaline membranes apparently contain globulins derived from the blood stream. I have never seen hyaline membranes in the lungs of rats who died of anoxia. I haven't seen too many hyaline membranes in the lungs of rats who died of hyperoxia. Guinea pigs form hyaline membranes.

BROWN: I think that hyaline membrane disease as seen clinically, is seen with metabolic acidosis. In the study from Glasgow, acidosis was the cause of death in spite of oxygen treatment. It is now time to turn to the discussion of Dr. Lambertsen's paper.

HAUGAARD: Could you tell us a little about some of your early experiments concerning intermittent exposure to high oxygen pressures?

LAMBERTSEN: I was trying to avoid things we had covered in the last symposium. However, in small animals such as guinea pigs, it seems to be possible to very promptly reverse the development of oxygen toxicity and thereby extend the tolerance to oxygen by interrupting exposure to high oxygen pressure. This is accomplished by alternating periods of breathing O_2 or high oxygen concentrations with periods of low oxygen tension. This procedure also minimizes exposure to high inspired inert gas pressures with practical gains in protecting against both oxygen toxicity and the bends.

HAUGAARD: That is a very significant experiment.

THOMAS: I was wondering if you could express your current opinion on CO_2 as being the possible primary cause of oxygen toxicity?

LAMBERTSEN: I have no such opinion. Actually in the phenomenon of oxygen poisoning there is an oxygen-related chemical reaction inside of the cells. There are in addition many other factors that determine the dose of oxygen at the reactive sites in the cell. These factors include such things as tissue blood flow, composition of the gas mixture, depth or pressure, and temperature. Such factors as intracellular pH may also affect certain enzyme reactions, and for such reasons CO_2 may be involved indirectly in oxygen poisoning at the cellular level in addition to its role in altering the delivery of oxygen to the cells. Certainly

molecular CO_2 is a narcotic and therefore it might alter even the electrical activity of cell membranes and thus modify convulsive behavior, even if it did not modify the actual development of oxygen poisoning. I can therefore visualize four or five different ways in which CO_2 must be involved in the over-all pattern of oxygen poisoning, but I do not want to discuss the old question of whether CO_2 is the primary cause of oxygen poisoning.

BEAN: An interesting point in relation to your answer is the demonstration of so-called protective reaction of CO_2. Chapin, and also Levi, some years ago did some work with high oxygen tensions. He found that when CO_2 was added to O_2 under pressure (10 per cent CO_2 at 3. atm) that animals did not convulse as violently as they did with O_2 alone. This is an addition to the now generally accepted view that CO_2 does potentiate the oxygen toxicity by increasing delivery of oxygen. Ten per cent at 3 atmospheres is comparable to 30 per cent CO_2 at atmospheric pressure. This may well represent a narcotic level of CO_2, with blocking of the response to oxygen toxicity.

RAHN: I am concerned about the comparisons people make between in vitro and in vivo systems in experiments on the effects of high oxygen tensions. We often compare results when a homogenate or an intact animal is exposed to 5 atmospheres of oxygen pressure. I have been impressed with some of the attempts that have been made to measure in vivo the oxygen pressure of the brain surface and further down in the brain substance. Po_2 deep in the brain may normally be as low as 10-15 mm Hg. If we then extrapolate this result to 5 atmospheres of oxygen, the Po_2 of the brain may be no higher than 100 mm Hg at 5 atmospheres pressure.

LAMBERTSEN: I know what Dr. Rahn is getting at since we have dealt with this same question before. In comparing in vivo and in vitro studies we should like to give attention to the Po_2 at the cells or to the reactions that are actually going to be poisoned, rather than to the ambient environment. We have studied the change in Po_2 across the human brain at various levels of inspired Po_2. If arterial blood enters the brain at about 2500 mm Hg Po_2, we will find something less than 100 mm Hg Po_2 in the brain venous blood. Certainly there are cells in the brain which have a still lower Po_2 than the 100 mm Hg found in the venous blood, even when delivery pressure in the arterial side is more than several thousand mm Hg. If we now look within the brain at one of the millions of capillary units, we can picture millions of different levels of Po_2, from the very high entering Po_2 at the arterial end of each capillary to a progressively lower tension in the blood passing through the capillary. It is probable that in regions of brain tissue where the removal of oxygen is high, one would have a rapid fall in Po_2 to a very low Po_2. Other regions, where O_2 removal is low, would have a high Po_2 on the venous side. Therefore, if it were truly possible to use electrodes to measure the specific local oxygen tension, a great variation would be found over minute distances. Practically, even with small electrodes, you get an average or conglomerate of these many Po_2 values. The absolute level of Po_2 which produces toxicity in vivo is not yet definable. We can not learn this by just measuring Po_2 in the brain or on the brain surface, because the Po_2 in the brain is a few million different Po_2 values at the microscopic level. Some cells are exposed to very, very high tensions and some to low.

BEAN: In probing the brain with O_2 electrodes I find that there is a great deal of difference from area to area. Theoretically, if you put a small electrode into the brain you ought to be able to get regional changes, even though not individual cellular changes. In these records, you will find that under oxygen high pressure there is a general increase in the oxygen tension or oxygen availability. Then, as oxygen exposure continues, there may be some decrease in Po_2. Finally, you find great elevations, specific elevations in multiple electrodes, which are not synchronous in different parts of the brain. They are different in intensity, different in direction, are completely out of phase, and sometimes associated with the convulsive seizure. We may therefore be mistaken in looking at one point in the brain when actually we should look at the whole brain in studies of oxygen poisoning. I do think that the oxygen electrode, in spite of its limitations, provides some very valuable information.

RAHN: I agree with you Dr. Bean. Could you give me a typical value for brain Po_2?

BEAN: About 200 per cent increase over resting values. One of the big difficulties, of course, in work with oxygen electrodes is calibration. This makes it necessary for much of the data obtained to be reported as change rather than in mm Hg.

When an animal breathing oxygen at 1 atmosphere is switched to 3 atmospheres, there is an increase of 300 to 400 per cent in oxygen tension in brain tissue. When bursts come, they may be even higher than that. I have interpreted these sudden alterations as indicative of changes in brain blood flow in various areas. Why should one area of the brain increase in flow so markedly over the other one? They do sometimes run parallel but there is this great difference in blood flow and, of course, you have local changes in CO_2, local changes in oxygen tension, and in pH, all of which have some influence on the animal.

JACOBSON: We have studied oxygen tensions in lymph and found that the oxygen tension was extraordinarily low. If one takes lymph as being one step closer than venous blood to the cellular site, this might provide another approach to the study of questions about the significance of Po_2 in arterial and venous blood.

HAUGAARD: There is considerable question whether one can honestly compare in vivo and in vitro experiments. Quite a few laboratories have studied the effects of oxygen on cells in tissue culture and have found that, even at sea level, about 50 per cent oxygen is toxic to the cells. The optimum oxygen tension (for diffusion) is about 20 to 30 per cent and if you go above that oxygen toxicity develops.

I think that Dr. Thomas would probably have found similar effects of oxygen on brain metabolism if he had used smaller pressures.

THOMAS: After talking with Dr. Haugaard I decided to work at 1 atmosphere and found effects of oxygen. Also some bacterial preparations give a toxic effect at less than 0.2 atmosphere pressure of oxygen.

BEAN: In about 1929 we worked with pneumococcus and under 5 or 6 atmospheres of oxygen there was no growth at all. Even at 0.5 atmosphere you could absolutely block out any growth of pneumococcus of a particular type. There have also been attempts made to preserve milk by use of oxygen high pressure, particularly in combination with CO_2.

MACKAY (S): I have an impression that Dr. Lambertsen's statement about alternating exposure to high and to normal Po_2 was not quite finished. In your proposal to cycle the oxygen pressure up and down, so that when the oxygen pressure is low the partial pressure of the inert gas is high, is it not true you would end up with the same decompression time anyhow?

LAMBERTSEN: In some situations, yes. However, I think it would have to be shorter because we are integrating the changes in nitrogen or other inert gas pressures.

MACKAY (S): Don't you also integrate the effects of the oxygen?

LAMBERTSEN: I do not believe so. Depending upon the cycling sequence there should be a complete or partial recovery from oxygen poisoning. For example, if you breathe oxygen today and then do not breathe it again until tomorrow, you can breathe it again the next day and still never be poisoned. Many of us have done this for several years of wartime oxygen diving. This is not an integral effect; this is a cure from any effects of the previous oxygen exposure. The rate of recovery from early oxygen effects appears shorter than the rate of development of toxicity. I would not like to make this appear simple, but there is much to be gained by extension of these studies.

CARPENTER: I am wondering whether the convulsive effects of oxygen might be accounted for on the basis of a depressant action? The activity of certain areas of the brain is normally controlled by inhibition, and neurophysiologists realize that the convulsive action of strychnine, and perhaps metrazol, is brought about by release of inhibition. I think Dr. Lambertsen alluded to a depressant action of oxygen, did you not?

LAMBERTSEN: Yes. There may be more than one such effect. One which we see is depression of the respiratory response to CO_2. Oxygen may possibly also act as an inert gas. Certainly we do not know whether the very prominent respiratory depression by O_2 is a central effect or is an action of O_2 on the chemoreceptor mechanism. It is very possible that it is a completely peripheral mechanism and not related to a narcotic or other depressant effect in the brain itself. It is important that oxygen does alter the respiratory drive. If there are other factors such as resistance to breathing, narcosis, etc. which alter the respiratory drive at great depth, these will all interact in the underwater environment. It is possible that the interacting effects may act in the same direction, toward a severe respiratory depression. Certainly we should not think of these effects as being all physical, or all chemical, or all central, or all peripheral. We are all cracking down these effects and it is going to take a rather meticulous job of physiological dissection. Sometimes this will require animal work and sometimes the type of chemical "dissection" our own experiments

have employed. We see the respiratory depressant effect of oxygen to be at least as great as that of a large clinical dose of morphine. It is a very prominent depression.

CARPENTER: The awkward aspect of any proposed depressant effect of oxygen on specific areas of the brain is that some of the fluorocarbon anesthetics do produce facial twitches and convulsive-like seizures, probably by a specific depression of an inhibitory mechanism. If you pretreat mice with nitrogen, the number, incidence and severity of the seizures that result from oxygen at high pressure diminishes. Therefore, the narcotic action of nitrogen will protect against seizures. This could still depend on a differential site of action.

GILLEN: I would like to complicate the existing confusion about oxygen and carbon dioxide. At sea level with a gas mixture of 35 per cent CO_2, 20 per cent O_2 and the balance N_2, the incidence of convulsions will be essentially 100 per cent. This is not oxygen toxicity. If you now increase the oxygen percentage, eliminating the inert gas, the incidence and severity of convulsions will be decreased. Marshall and Lambertsen showed that, as you increase the Pco_2 to extreme levels, it is possible to prevent the occurrence of oxygen convulsions entirely. Pretreatment of small animals with TRIS buffer protects them against oxygen convulsions. Conversely, pretreatment with the carbonic anhydrase inhibitor, acetazolamide (Diamox), the susceptibility to oxygen convulsions is increased.

COWLEY: We have been surprised, in treating hypovolemic shock in dogs, that severely shocked dogs developed oxygen convulsions in spite of the need for oxygen.

LAMBERTSEN: There is a great deal of physiological implication in the comments by Dr. Gillen and Cowley. This is not confusion, but normal complication. It is necessary to consider and study the nature and location of acid-base influences upon oxygen toxicity. It is also necessary to be aware that hyperoxia and hypoxia can coexist in the same organ at the same time.

VAN DER AUE: A number of observations suggest an important relation of the circulatory state to diving problems. Oxygen toxicity produces a circumoral pallor suggesting peripheral vasoconstriction. Then, in testing borderline decompression tables for prevention of bends we have found that elevation of CO_2, by exercise or by CO_2 administration, leads to an increased bends incidence. Greater bends incidence is also found after diving in warm water than after diving in cold water. Each of these observations suggests that there are practical conditions in which blood flow and nitrogen uptake are related. I have wondered whether the same thing may not apply to the development of oxygen toxicity such that with work or increased CO_2, vasodilatation leads to increased access of oxygen to the tissue.

BEAN: That comment goes back to Dr. Lambertsen's earlier work on brain circulation at high oxygen pressures, and some of our own work. We did studies on rats years ago in which we hyperventilated rats and found that hyperventilating gave a very distinct measure of protection. This has also been found in dogs at EDU many years ago.

LORD: We have studied the effect of high pressure on the recovery of dogs from electrically induced ventricular fibrillation. We put dogs in a chamber with 100 per cent oxygen in an attempt to increase the duration of fibrillation following which we could return the dogs to normal sinus rhythm. We found no protective effect of ventilation with high pressure oxygen at 4 atmospheres. Dogs treated with hypothermia in addition to oxygen did have a lower death rate than dogs treated with hypothermia alone or with oxygen alone.

BEAN: Levi and his group also found that there was an additional protection with hypothermia with high oxygen pressure, but not very much. Are there other questions?

LAMBERTSEN: When are we going to have lunch?

BEAN: With that we will adjourn.

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MEASUREMENT OF INERT GAS NARCOSIS IN MAN

C. M. Hesser
Laboratories of Aviation and Naval Medicine
Department of Physiology
Karolinska Institutet, Stockholm, Sweden

Numerous investigations have shown that air at raised barometric pressures exerts certain mental and phychomotor effects on man, such as euphoria, confusion, slowed mental activity, motor incoordination, and impairment in performance. Behnke, Thomson and Motley[1] who were the first to attribute these effects to the high partial pressure of nitrogen, contended that subjective intoxication may occur at pressures as low as 3.0 atm abs (atm). This corresponds to a diving depth of about 60 feet. Kiessling and Maag[2] have recently reported that changes in objective performance are demonstrable at 4.0 atm. Case and Haldane[3] also ascribing the narcotic action to nitrogen excess, found, on the other hand, that at pressures as high as 8.6 atm there was only a slight intoxication with no reduction in manual dexterity. They also made the important observation that minimal amounts of carbon dioxide in the inspired air greatly increased the deterioration in performance at raised pressure. Damant[4] attributed part of the intoxicating effects to the increased oxygen pressure.

Bean[5] and Buhlmann[6] have expressed doubt that nitrogen is responsible for compressed air narcosis, and have contended that the sole causative factor is a rise in body CO_2 tension. Increased breathing resistance due to raised gas density at pressure would result, according to Buhlmann, in hypoventilation and impaired CO_2 elimination. Bean reasoned that raised gas density would lead to increased difficulty in CO_2 diffusion and mixing in the alveoli and in this way to reduced CO_2 output.

Finally, it has also been suggested that the subjective symptoms experienced in work at high atmospheric pressure are manifestations of anxiety[7] and claustrophobia, or are caused either by a combination of all of the aforementioned factors or else by the pressure itself[9].

However, as evidenced from recent encephalographic studies of Bennett and Glass[10] there seems to be no doubt that high nitrogen pressure constitutes an important causative factor of compressed air narcosis. At atmospheric pressure the solving of arithmetical problems blocked the occipital alpha rhythm in subjects of the "responsive" or R type. No such blocking occurred after a variable time at increased air pressure, indicating that a fundamental change occurs in the central nervous system when a certain tension of nitrogen is reached. If nitrogen in the inspired air was replaced by helium, no abolition of blocking took place.

The divergent opinions as to the mechanism of compressed air narcosis may to some extent be explained by the fact that, at raised barometric pressures, there are simultaneous increases in alveolar oxygen pressure, alveolar nitrogen pressure, and gas density. Experimental situations in which the subjects are exposed merely to "normal" air at different barometric pressures will therefore

not permit any differentiation between these factors as to their possible narcotic effects.

In collaboration with Drs. M. Frankenhaeuser and V. Graff-Lonnevig we have made an attempt to separate the possible factors responsible for compressed air narcosis by studying the changes in human performance induced through exposure to different nitrogen-oxygen gas mixtures at increased ambient pressures*. For this purpose 12 young subjects were tested individually on three psychomotor tasks while breathing different gas mixtures at normal and at raised pressures in a dry compression chamber. To exclude admixture or expired carbon dioxide, all gas mixtures were inhaled from Douglas bags via a low resistance and small dead space (about 10 ml) breathing valve. The conditions were as follows:

TABLE I

Condition	Ambient pressure (atm abs)	Inspired gas mixture	Partial pressures of inspired gases (atm abs)	
			Oxygen	Nitrogen
A	1.0	Air	0.20	0.74
B	1.0	100% O_2	0.94	—
C	4.2	5.2% O_2 in N_2	0.22	3.92
D	5.0	Air	1.03	3.91
E	6.6	39.8% O_2 in N_2	2.60	3.94

Tests for simple and four-choice visual reaction times and mirror drawing were used. The task on mirror drawing was to move a stylus as fast as possible along a track, cut out in a metal plate so as to form a five-pointed star, and visible only in a mirror. The track was provided with saw-tooth notches which tended to catch the stylus. The time score was the time spent to complete one run, and the error score the total time of contact between the stylus and the metal contours of the track. The five conditions and the tasks within each condition were rotated at random order. At least four to five minutes were allowed to pass after any change in ambient pressure or of inhaled gas mixture before a test series was started.

The results obtained in the five conditions are presented in Table II. A rise in air pressure from 1.0 to 5.0 atm caused only a slight tendency toward impaired performance (a two to three per cent increase in simple and choice reaction times). These observations agree with those of Case and Haldane[3] but

*A full account of the present work will be published in Acta physiol. Scand.

TABLE II

Time and Error Scores in Psychomotor Tasks
(mean values for 12 subjects)

Task	Condition A Air, 1.0 atm	B O_2, 1.0 atm	C 5.2% O_2 in N_2, 4.2 atm	D Air, 5.0 atm	E 39.8% O_2 in N_2, 6.6 atm
Simple reaction, sec	0.243	0.242	0.241	0.248	0.256
Choice reaction, sec	0.671	0.683	0.685	0.691	0.698
Mirror drawing, time, sec	9.16	9.25	9.47	9.24	8.93
Mirror drawing, error sec	2.89	2.85	3.39	3.11	3.34

are at variance with those of Shilling and Willgrube[9] and Kiessling and Maag[2], who at approximately the same pressures observed a significant 10 and 21 per cent increment in simple and two-choice visual reaction times, respectively. These quantitative deviations in results may possibly be due to pronounced individual differences in susceptibility to air narcosis or to differences in the general experimental procedure. Since the addition of even minimal amounts of carbon dioxide to the inspired air may greatly enhance the narcotic action of air at pressure[3], the effects observed in deep-sea divers and in subjects breathing air in a compression chamber might in part be due to the carbon dioxide that accumulates in the diver's helmet or in the chamber.

That pure air at 5.0 atm pressure produced only slight changes in objective performance in resting subjects is not inconsistent with the observations of Behnke et al[1] that subjective intoxication may occur at pressures as low as 3.0 atm. In experiments dealing with the effects of nitrous oxide and other drugs on various mental functions, Frankenhaeuser et al[11,12,13] found that performance may remain relatively undisturbed even when subjective changes are pronounced.

If oxygen was added to the inspired air (39.8% O_2 in N_2 at 6.6 atm), the impairment in performance became more marked, indicating a synergistic rather than antagonistic action of nitrogen excess and oxygen excess. From this it may be concluded that compressed air narcosis is not due to interference with oxidation in the tissues by nitrogen under high pressure.

By comparing the data obtained at pressure (Conditions C, D and E), the effects of increasing the oxygen pressure at a constant nitrogen pressure of 3.9 atm were determined. As shown in Figure 1, the changes in performance increased with increasing oxygen pressure, and reached a statistically significant level ($P < 0.05$) in two of the tasks when the rise in oxygen pressure amounted to

2.4 atm. This observation supports the view that oxygen excess has a potentiating effect on compressed air narcosis.

In a previous investigation we found that increasing the oxygen pressure to 3.0 atm at a low nitrogen pressure had but very slight effects on performance[14]. The effects of oxygen thus seem to be more marked under conditions of high nitrogen pressure. Our present data do not allow any definite conclusion as to the immediate cause of the observed differences in oxygen effects.

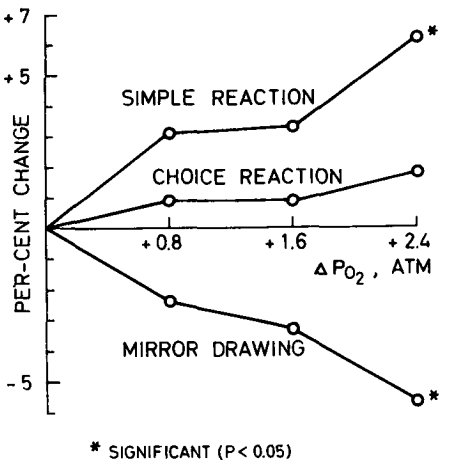

Figure 1. Changes in Performance Induced by Increasing the Oxygen Pressure at a Constant High Nitrogen Pressure (3.9 atm) (mean values for 12 subjects)

It seems possible, however, that oxygen excess may act indirectly by interfering with carbon dioxide elimination from the tissues. This conclusion is based on the following reasoning. Lambertsen and co-workers[15,16,17] found that the inhalation of oxygen at 3.0 -3.5 atm caused an increased activity of the respiratory center due to local accumulation of carbon dixoide, a 5-6 mm Hg fall in alveolar and arterial P_{CO_2}, and a 3 mm Hg increment in internal jugular P_{CO_2}. This indicated that the CO_2 tension in the respiratory center also increased by about 3 mm Hg. To induce a similar rise in internal jugular P_{CO_2} by carbon dioxide breathing at normal atmospheric pressure, the inspired CO_2 tension would have to be increased to about 20 mm Hg. However, a similar rise in the inspired CO_2 tension causes a marked impairment of performance at 10 atm but no deterioration in manual or arithmetical skill at normal atmospheric pressure[3].

From these observations it may be inferred that 1) an increase in inspired P_{O_2} to higher than normal levels causes a rise in tissue P_{CO_2}, 2) high N_2 and CO_2 tissue tensions have a synergistic narcotic action and 3) an isolated, moderate increase in tissue P_{CO_2} has no demonstrable narcotic effect. These three statements would seem to be compatible with our findings that, at a high P_{N_2} level, the performance changes increased with increased inspired P_{O_2}, whereas at a low P_{N_2} level a similar increase in inspired P_{O_2} had no significant effect on performance.

By comparing condition C with A, and D with B, the effects of raising the nitrogen pressure alone were revealed. From the results of these comparisons it may be concluded that, at rest, nitrogen pressures up to 3.9 atm have but very slight effects on objective performance. Similarly, in a previous investigation on breath-holding at elevated pressures, we have obtained evidence that nitrogen pressures below 4.0 atm have little if any narcotic effect on the respiratory center[18].

The view that compressed air narcosis is caused solely by a rise in the alveolar and tissue CO_2 tension due to hypoventilation or increased difficulty in CO_2 diffusion in the lungs may hold for rapid compression. For "steady state" conditions, however, this hypothesis is contradicted by recent observations on the CO_2 output and alveolar Pco_2 in man at elevated pressure.

In resting subjects after 15 min air breathing at 3.5 atm, Lambertsen et al[17] found no reduction in CO_2 output and a slight fall in alveolar Pco_2, implying alveolar hyperventilation rather than hypoventilation. The last-mentioned observation was confirmed by Hesser and Holmgren[19], who also reported that when the nitrogen pressure alone was increased to 3.8 atm, the alveolar ventilation decreased somewhat. Evidence was presented that this suppression of ventilation was caused by the increase in gas density and breathing resistance rather than by any depressant action of high nitrogen pressure on the respiratory center. It was also concluded that the increase in alveolar ventilation observed during air breathing at 4.0 atm was due to the respiratory stimulating effect of high Po_2 being greater than the suppressing effect on ventilation of increased breathing resistance.

At present it cannot be ascertained whether the same relationship between these two opposing effects on respiration prevails at air pressures higher than 4.0 atm and/or during muscular exercise. It seems possible that, in moderate and heavy exercise at elevated pressure, the increment in respiratory minute volume would result in a marked rise in breathing resistance and, hence, in a suppression of ventilation and a consequent rise in body CO_2 tension. If one assumes a synergistic narcotic action of N_2 excess and CO_2 excess, this mechanism, together with an increase in inspired Pco_2 due to accumulation of CO_2 in the helmet, might well explain the marked symptoms of compressed air intoxication that divers usually experience at great depths.

Investigations currently being performed by Adolfson in our laboratory support the hypothesis that muscular exercise might enhance the impairment of performance observed at raised air pressure. This is apparent from Figure 2, which shows that, with increasing ambient pressure, the loss in manual dexterity was much greater during exercise than at rest.

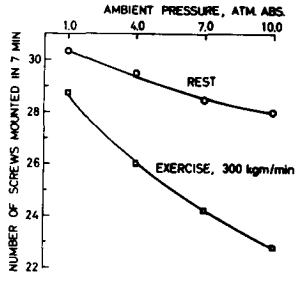

Figure 2. Effects of Raised Barometric Pressures on Manual Dexterity (screw-test at Rest and during Exercise (bicycle) (mean values for 10 subjects)

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NEUROPHARMACOLOGIC AND NEUROPHYSIOLOGIC CHANGES IN INERT GAS NARCOSIS

P. B. Bennett
Royal Navy Physiological Laboratory
Alverstoke, Hants, England

It is well known that helium and hydrogen are effective substitutes for nitrogen[1,2,3] if deep diving is to be performed without the appearance of the signs and symptoms characteristic of inert gas narcosis[4,5,6,7]. Little attention, however, appears to have been paid to the protection that drugs may afford or the indication such experiments might give as to the mechanism of the narcosis.

The drug Frenquel [alpha (-4 piperydyl) benzhydrol hydrochloride] (Merrel-National Labs, Ltd.) has been produced for the control of psychotic hallucinations and behavior disturbances. It is neither a tranquillizer nor a central nervous system stimulant and is said to be safe to use without fear of tolerance, toxicity or side effects, even at very high dosage[8,9].

The response of 36 Wistar rats to a minimal electric shock was used in 92 experiments to measure the extent of the narcosis produced by 180 psi argon and nitrogen, before and after Frenquel administration[10].

With this technique, a rat was placed in a cage the metal base of which acted as an electrode and the animal's tail was attached to a second electrode. The voltage of a square wave stimulus across the electrodes was increased until a minimal but definite twitch of the caudal muscles was obtained. The percentage increase in the voltage required to elicit the same response at increased pressures was taken to indicate the level of narcosis.

To establish that the method gave a reliable indication of the narcotic state of the animals, rats were exposed to raised partial pressures of argon, nitrogen and helium with and without small quantities of carbon dioxide. The results were in agreement with the facts widely known about inert gas narcosis. The rats were more narcotized when breathing argon than with nitrogen and required a significantly greater increase in voltage to elicit a stimulus. Nitrogen in turn was more narcotic than helium[4,5]. The presence of small quantities of carbon dioxide further increased the severity of the narcosis[5] as indicated by a still greater increase in voltage.

In Figure 1 is shown the effect of 20 mg and 40 mg oral doses of Frenquel given to four rats at 180 psi nitrogen. After a 48 hour delay the 40 mg dose afforded complete protection and the mean stimulus voltage was not significantly different from rats at atmospheric pressure. The 20 mg dose afforded a substantial improvement.

In other experiments the mean voltage increase for 12 rats at 180 psi nitrogen without Frenquel was $50.2\% \pm 4\%$. Forty-eight hours after 40 mg oral Frenquel the mean voltage increase of $1.21\% \pm 2.45\%$ was not significantly different from that at atmospheric pressure. Of significant interest was the observation

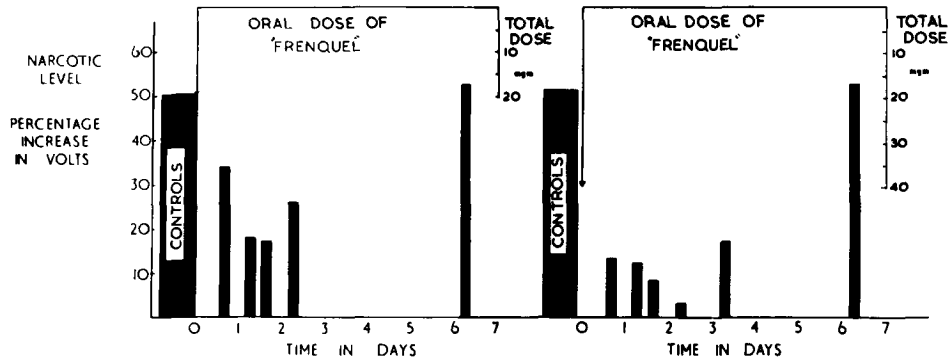

Figure 1. Effect on Mean Response Index of Oral Doses of 20 mg and 40 mg Frenquel on Four Rats at a Nitrogen Partial Pressure of 180 psi Compared with 12 Control Animals.

that the 40 mg oral dose was also found to be effective for four rats breathing argon at the same partial pressure of 180 psi (Figure 2). Yet this produces a mean voltage increase of some 150% (seven rats) compared with only 50% (12 rats) for nitrogen.

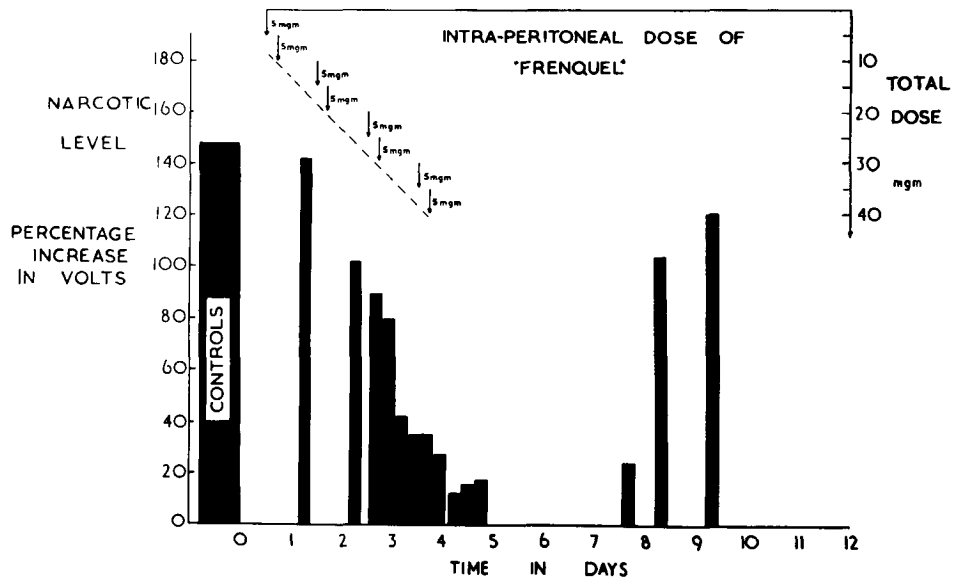

Figure 2. Effect on Mean Response Index of 40 mg Frenquel on Four Rats at an Argon Partial Pressure of 180 psi Compared with Seven Controls.

Ebert, Hornsey and Howard[11] on the basis of oxygen dependent radiosensitivity studies, concluded that the mechanism for production of inert gas narcosis was a displacement adsorption of oxygen associated with lipid material either in the nuclear membrane or within the nucleus of the cell itself. More recently Schreiner et al[12,13] have also suggested a mechanism of histotoxic hypoxia. However, there are many other possibilities as shown by Pittinger and Keasling[14] and Butler[15] in their reviews of mechanisms of anaesthesia and narcosis. It may well be that not one but a number of the suggested factors such as diffusion, oil solubility, permeability, molecular dimensions, metabolism, adsorption, hypoxia or asphyxia are involved.

How therefore Frenquel, or indeed any other drug, is able to prevent inert gas narcosis must await a clearer understanding of its cause. Nevertheless since Frenquel was effective in controlling inert gas narcosis in rats, preliminary investigations were made into its ability to prevent the narcosis found in three men breathing compressed air at 10 atmospheres absolute[16].

The tests of narcosis used were arithmetic of the two figure by one figure multiplication type[17], specific letter cancellation in a printed script and a visual-motor coordination test, in which the subject inserted with forceps as many steel balls as possible into a vertical tube in 40 seconds. The three subjects tested also made notes of their subjective sensations. Frenquel was administered orally in daily doses of 10 mg, 300 mg or 900 mg for a period of seven days.

The 100 mg and 300 mg experiments showed little evidence of a protective capacity for the drug and there was evidence of interference by acclimatization and learning factors.

With the 900 mg dose, the subjects were compressed and tested for 14 days prior to administration of the drug in an endeavor to overcome these factors. This was reasonably successful and a mild anti-narcotic action appeared likely at this dose strength giving a 33% improvement in test performance. Subjective sensations of narcosis were, however, still evident and side effects due to the drug were reported after a total dose of 4,500 mg. As no placebo was used in these ad hoc experiments it is possible these effects are exaggerated. More elaborate experiments would clarify this.

For one subject the dose of Frenquel was increased to 1200 mg a day for three days and the critical fusion frequency (cff) used as the test for narcosis. Previous work[18,19] has shown that this threshold is affected by high pressures of inert gases.

Compression with air to 300 feet caused a significant rise in the cff (Figure 3). After a total dose of 3600 mg this rise did not occur. Again some side effects were observed but they appeared less obtrusive than in previous experiments. The subjective sensations of inert gas narcosis were well controlled.

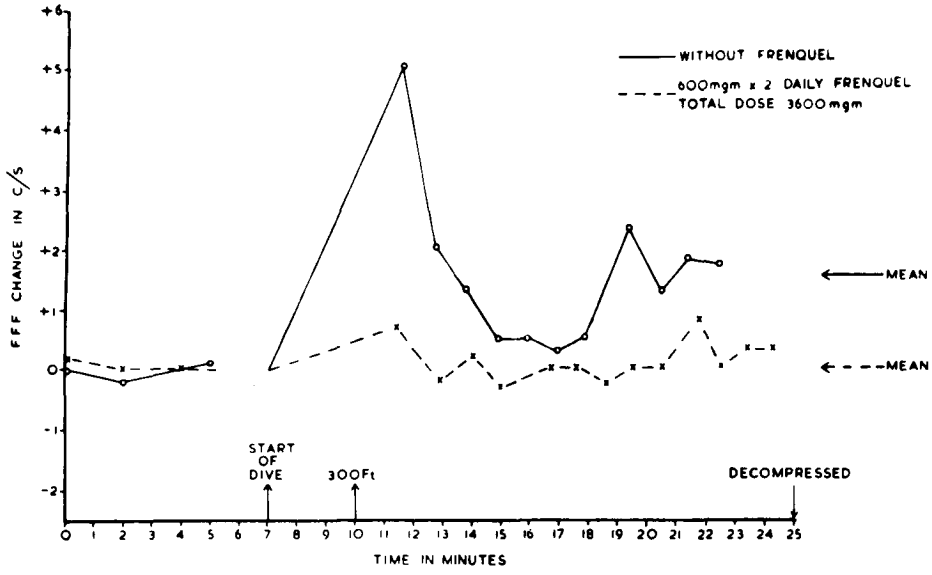

Figure 3. Critical Fusion Frequency at 300 Feet Before and After Frenquel Administration.

As with the rat experiment, there was evidence of a delay in the protective action but intravenous administration would probably shorten this. Further investigations are required on a larger scale, however, before any definite conclusions may be made as to the practical value of this drug in man.

Other experiments[20] examined a number of other drugs in animals. Previous work on the effect of various rates of compression on rats exposed to different oxygen-nitrogen mixtures[21] suggested that both oxygen and nitrogen may produce their toxic effects in a similar or at least related manner. Experiments were therefore designed to examine the effects of 11 drugs on rats exposed to nitrogen narcosis and oxygen poisoning.

The sensitivity of the rats to a nitrogen partial pressure of 180 psi was determined by the electric shock technique previously described. Sensitivity to oxygen was determined by measurement of the time to convulsions at 80 psi. The drugs were administered intraperitoneally or orally five to ten minutes prior to compression with the exception of Frenquel which was given 48 hours beforehand.

It is apparent that drugs which prevent inert gas narcosis are able to exert a similar protective action against oxygen toxicity and vice versa (Figure 4). Of singular interest was the observation that the protective drugs are primarily antipyretics, sedatives or hypnotics, whereas the aggravating drugs are stimulants or convulsants. This suggests the process of narcosis may be active. Such an active process has been suggested for the action of low concentrations of sodium cyanide (0.2 mg/kg), which produces a histotoxic hypoxia and increases the metabolism of the central nervous system in the production of central

inhibition[22]. Similar mechanisms might prevail for the production of inert gas narcosis. Experiments carried out recently suggest that the mechanism could be one of a maintained neuronal depolarization, primarily affecting synaptic transmission as is found with ether. The effect of raised pressures of argon, nitrogen and helium were examined on nembutalized rats' sciatic nerves and spinal synapses in vivo.

DRUG	MEAN % VOLTS INCREASE 180 lb. N_2/15 lb. O_2	MEAN CONVULSION TIME 80 lb. O_2	ACTION
NO DRUG	50 %	22 MINS.	—
CARBACHOL	0	58	PROTECTS
FRENQUEL	2	35	
DORIDEN	3	33	
PHENACETIN	5	48	
ASPIRIN	28 .	32	
PHYSOSTIGMINE	49	20	NO CHANGE
ADRENALIN	53	22	
SCOPOLAMINE	60	30	ENHANCES
METHEDRINE	75	15	
MEGIMIDE	77	15	
LEPTAZOL	87	9	

Figure 4. Effect of 11 Drugs on Inert Gas Narcosis and Oxygen Toxicity.

No significant change was observed in the action potentials of the sciatic nerve, even at 220 psi argon over one hour (Figure 5). This was not surprising considering the previous work of Carpenter[23,24,25,26] who found that blockade of isolated rat nerve required pressures in excess of 300 atmospheres.

On the other hand, synaptic potentials recorded at the sciatic nerve as a result of stimulating electrodes inserted into the fifth and sixth lumbar vertebrae were depressed by raised pressures of inert gases confirming earlier in vitro work[23,27].

Control records showed a characteristic pattern (Figure 6) which did not change unduly over one hour. The initial positivity after the stimulus artifact at 1 is a consequence of recording in volume and signifies the arrival of an impulse at the spinal cord. The negative spike 2 immediately following is of presynaptic primary afferent origin[28] and is followed by the high voltage negative potential at 3 representing postsynaptic interneuronal activity. Finally there is a

positive potential of equally high voltage which is also of postsynaptic origin possibly from the motoneuron.

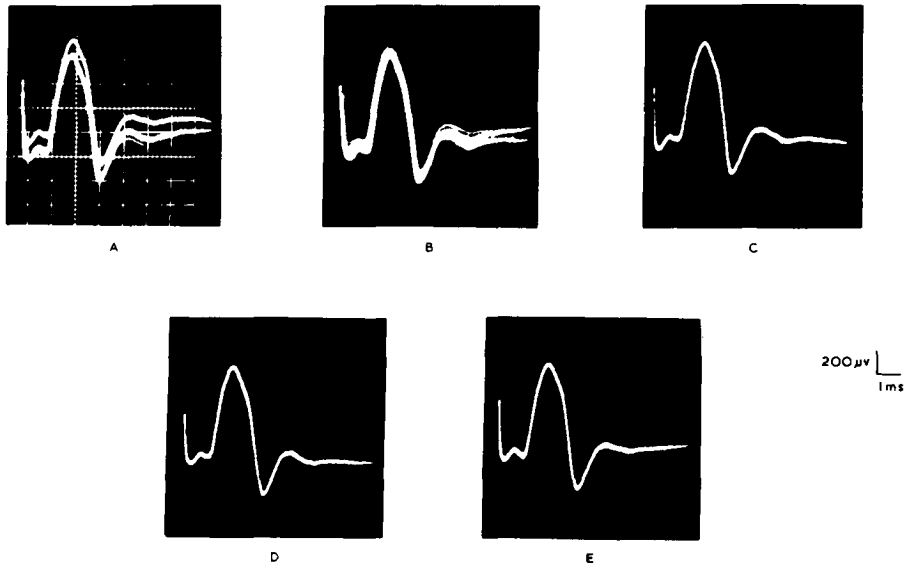

Figure 5. Rat Peripheral Nerve Conduction at 220 psi Argon/15 psi Oxygen. A atmospheric pressure, B after 15 minutes at pressure, C after 30 minutes, D after 45 minutes, E after 60 minutes at pressure.

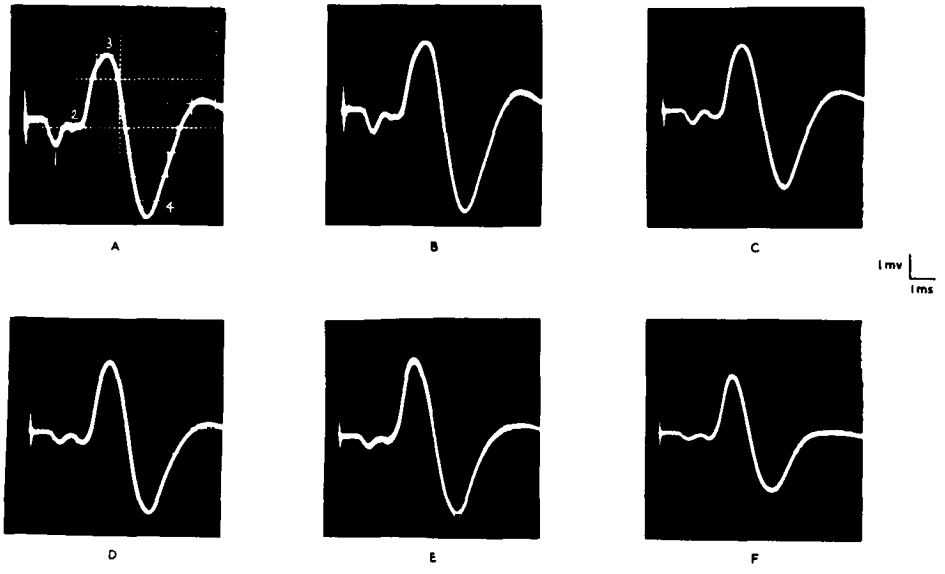

Figure 6. Rat Spinal Synaptic Conduction at Atmospheric Pressure. A 1 minute, B after 10 minutes, C after 15 minutes, D after 20 minutes, E after 30 minutes, F after 60 minutes.

At an argon partial pressure of 220 psi with 15 psi oxygen present there was an initial depression of the potentials (Figure 7B) followed by a period of augmentation (Figure 7C) and then a progressive depression and sometimes conduction block. The time after compression at which these events occurred and their severity depended on the partial pressure and nature of the inert gas. Nitrogen was less potent than argon and helium mixtures had no effect.

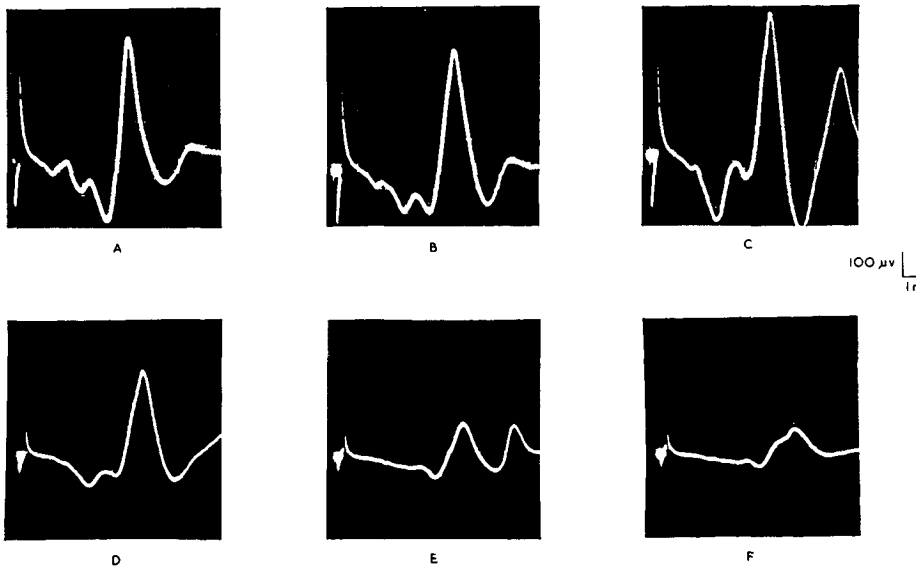

Figure 7. Rat Spinal Synaptic Conduction at 220 psi Argon/15 psi Oxygen. A atmospheric pressure, B 5 minutes at pressure, C 8 minutes at pressure, D 13 minutes at pressure, E 16 minutes at pressure, F 20 minutes at pressure.

In Figure 8 is shown the effect of 220 psi argon with 15 psi oxygen in greater detail. It may be seen that the second negative wave of postsynaptic origin in the first potential affected by the inert gas (Figure 8B). Shortly after it is blocked (8C) the presynaptic potential is augmented (8D, 8E). Gelfan and Tarlov[28] do not regard this as a true hyperpolarization but to be due to intensification of the current sink responsible for the presynaptic response as a consequence of the spreading block which has reached the afferent fibres proximal to the electrodes. Figure 8F shows the potentials shortly after decompression was started.

These changes are similar to those produced by asphyxia or hypoxia[28] and could be due to either a histotoxic hypoxia and retained carbon dioxide or a histotoxic hypoxia alone. Synapses therefore seem especially sensitive to raised pressures of inert gas. Previous electroencephalograph work on man[29] has pointed to the multisynaptic reticular formation as a part of the central nervous system highly susceptible to inert gases. In further confirmation experiments have recently been carried out in which 27 chloralosed cats (45-50 mg/kg) were

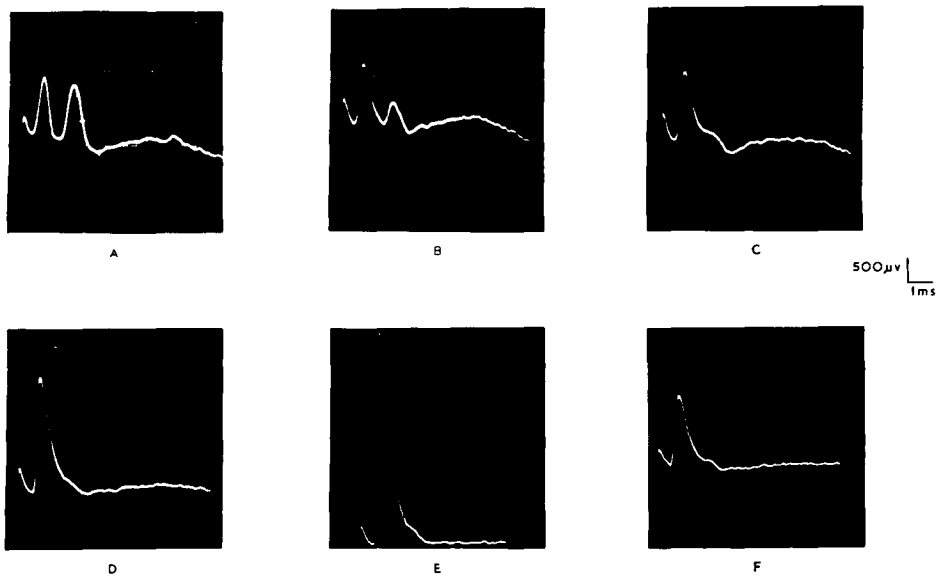

Figure 8. Rat Spinal Synaptic Conduction at 220 psi Argon/15 psi Oxygen. A atmospheric pressure, B after 8 minutes at pressure, C after 15 minutes at pressure, D after 18 minutes, E after 22 minutes, F after 27 minutes.

exposed to 150 psi argon, nitrogen and helium in the presence of 35 psi oxygen and auditory induced potentials evoked in the mesencephalic reticular formation and cerebral cortex.

At the cortex the positive potential, attributed to expression of the activity of the soma of deep cortical cells[30] shows first an augmentation followed by a gradual depression to a more or less steady state; whereas the negative cortical potential attributed to apical dendrites and also possibly superficial soma[31] shows a steady depression. The positive potential of the reticular formation is also steadily depressed. Using the technique of advancing means the relative heights of the evoked spikes may be compared in the cortex and reticular formation as an indication of the excitability of these parts of the central nervous system. As may be seen in Figure 9, where the positive cortical potential is compared with the negative potential of the brain stem, the latter is more severely depressed than the former. The negative cortical potential is depressed to the same extent as that of the brain stem. It may therefore be inferred that the primary action of inert gases, like many gaseous anaesthetics[32,33], is on cortical apical dendrites and the multisynaptic, mesencephalic reticular formation.

The initial cortical hyperexcitability shown by the positive potential may be due to the first effect of inert gases being on inhibitory neurons[34]. Alternatively it may be due to a cerebral vasodilatation as a result of asphyxia or the rise in chamber temperature during compression.

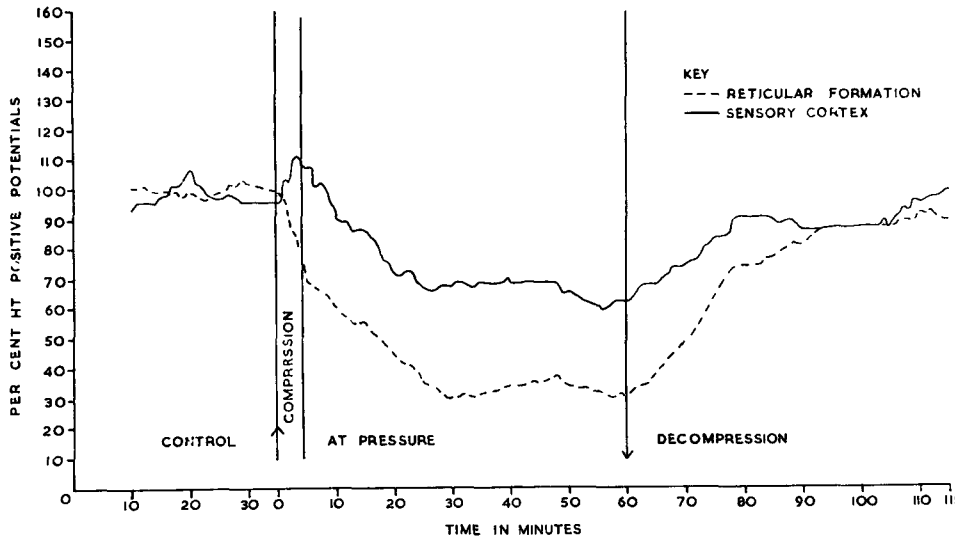

Figure 9. Comparison of the Advancing Means of Positive Auditory Evoked Potentials in the Cat Sensory Cortex and Mesencephalic Reticular Formation of the Brain Stem at 150 psi Argon/35 psi Oxygen Absolute.

As in the field of anaesthesia, to which inert gas narcosis appears closely connected[35], various workers support different mechanisms for its production. That retained carbon dioxide might be the cause was first suggested in 1932[36] and has since received experimental[37] and theoretical support[38,39]. Other workers, however, have refuted this hypothesis[17,40].

Most of the experimental work has relied on alveolar or blood P_{CO_2} or pH measurement, which may often move independently of brain P_{CO_2} and pH[41,42]. In an endeavor to define whether the carbon dioxide or nitrogen theory was correct or if perhaps both factors were involved, experiments have been carried out on 35 chloralosed cats at increased pressures of argon, nitrogen and helium and the cortical available oxygen (aO_2) and carbon dioxide tension (P_{CO_2}) measured.

The aO_2 was measured polarographically with a naked platinum and silver-silver chloride electrode at an applied voltage of 0.6 volts. The cortical P_{CO_2} was measured with a modified Severinghaus electrode. Control experiments on dead animals showed the electrodes to be stable and reliable at increased pressures. The electrodes were calibrated before and after use to ensure that there had been no change in their characteristics.

Auditory evoked cortical potentials were used to assess the extent of narcosis present.

Initial experiments examined the effect of 130 psi inert gas and 35 psi oxygen, measurements being made every three minutes. At atmospheric pressure over a period of 180 minutes the aO_2 showed no significant variation (Figure 10). However, breathing 100 per cent oxygen caused a rise in aO_2 of 70 to 100 per cent. During compression by admission of 20 psi O_2/130 psi inert gas there was further rise in aO_2, which then fell to much lower values when compression had ceased.

Helium induced the greatest rise in aO_2 at pressure. The nitrogen mixture showed a lower level and argon lower still. It was also observed that compression with 35 psi oxygen alone caused an aO_2 similar to that found with the helium-oxygen mixtures. Certainly the oxygen values for the nitrogen and argon mixtures were well below this value.

If the active process suggested by the drug and other experiments is a valid mechanism for the production of inert gas narcosis it might perhaps be expected that the more narcotic the gas the more oxygen is utilized as appears to be the case. Alternatively the low aO_2 could be due to impairment of ventilation as a consequence of the increased density of the breathing mixture.

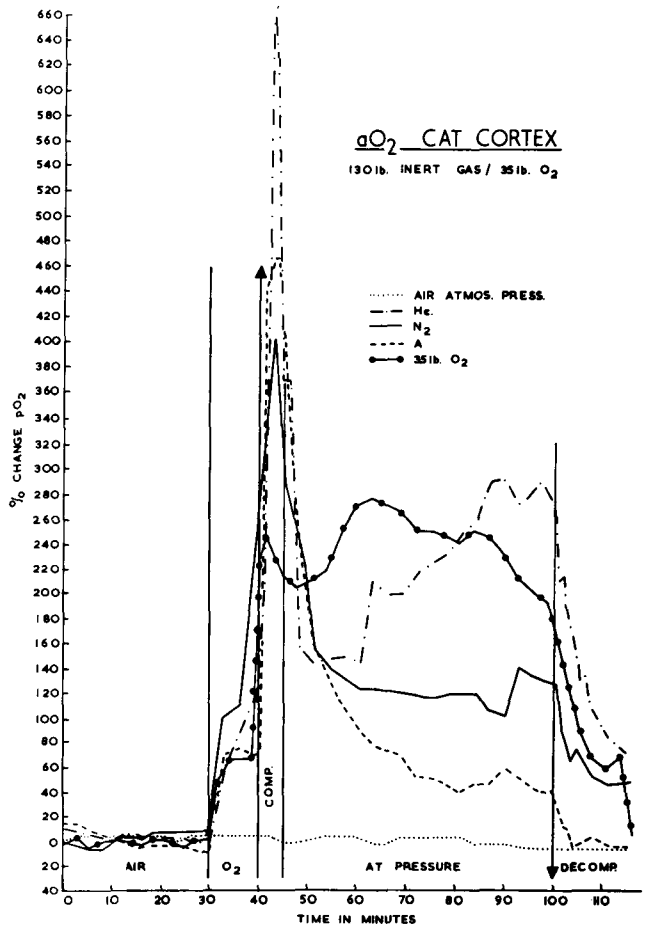

Figure 10. Cat Cortical Available Oxygen at Increased Pressures of Argon, Nitrogen, Helium, Oxygen and at Atmospheric Pressure. Complete decompression results are not given.

If the latter is true, a rise in cortical carbon dioxide tensions might also be expected with the various mixtures. Slight rises were in fact observed (Figure 11). The slow rise in Pco_2 seen with the controls was no doubt due to the chloralose anaesthetic.

At pressure helium induced no significant change in Pco_2, nitrogen a slight increase and argon a significant rise. This difference is presumably also

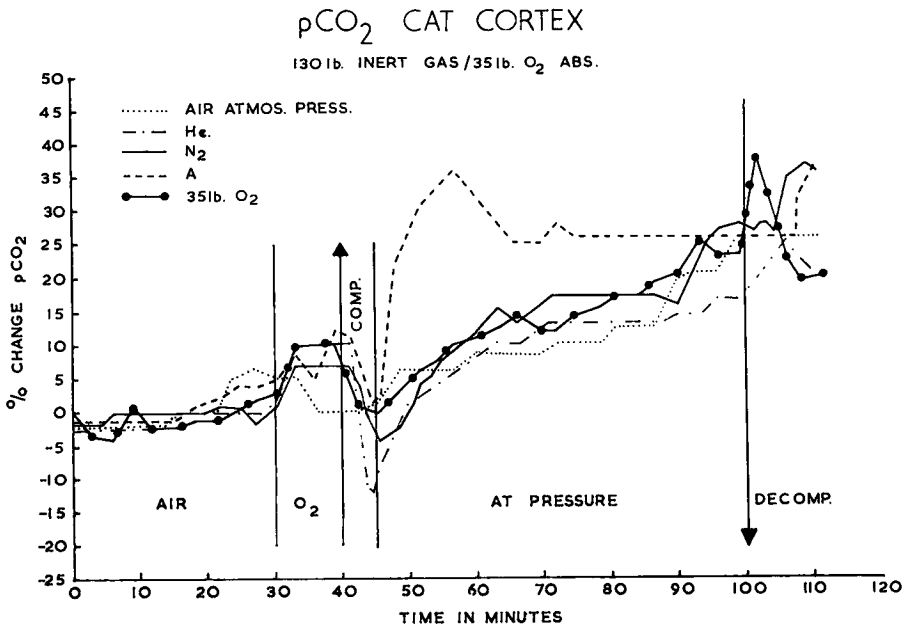

Figure 11. Cat CorticalCarbon Dioxide Tensions at Increased Pressures of Argon, Nitrogen, Helium, Oxygen and at Atmospheric Pressure. Complete decompression results are not given.

due to either changes in metabolism or density factors. However, with the exception of the rather dense argon, the precentage increase in Pco_2 is not materially different from cats exposed to 35 psi oxygen alone.

The fall in Pco_2 and rise in aO_2 during compression is possibly a consequence of vasodilatation as experiments in which the chamber temperature was increase by 10°C without compression produced similar changes. Such a vasodilatation could also account for the initial period of increased cortical excitability described previously.

It appeared that the increase in Pco_2 was due to high oxygen partial pressure of the mixtures as much as to their densities. Experiments were therefore performed where the oxygen partial pressure was not increased but the animals were exposed to the same pressure as previously. This meant a slight compensatory increase in the partial pressure of the inert gas. The aO_2 now did not show such a massive initial rise during compression (Figure 12). Further, all the mixtures caused a fall in aO_2 below normal values. The fact that helium also produced such a change was unexpected, especially as EEG examination of the auditory induced evoked potentials showed that unlike argon and nitrogen there was no narcosis present with the helium mixture.

However, Leon and Cook[43] have suggested that oxygen-helium mixtures will induce an increase in metabolism as a consequence of the marked loss of

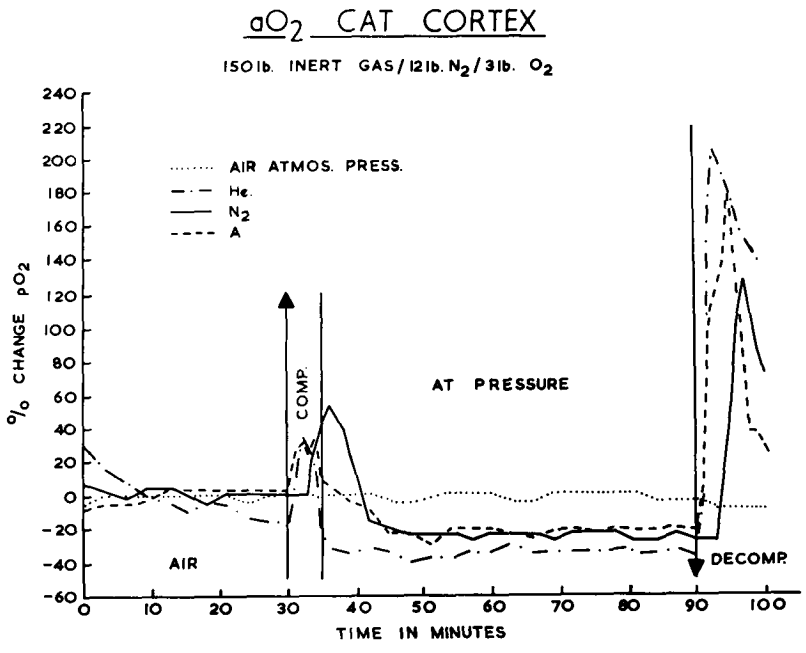

Figure 12. Cat Available Oxygen at Increased Inert Gas Pressures Without an Accompanying Increase in Oxygen Partial Pressure as in Figure 10. Complete decompression results are not given.

body heat of animals in helium due to its high conductivity of heat. The depression of aO_2 for nitrogen and argon is about the same but cannot be due to increased metabolism due to loss of body heat. It could, however, be due to an increased metabolism as a consequence of a histotoxic hypoxia[22] or respiratory embarrassment. If the latter were true, some graded aO_2 levels might have been expected depending on the density of the mixture.

The rise in aO_2 at the start of decompression was due to the addition of 20 - 30 psi oxygen to prevent anoxia during this phase.

As might be predicted the Pco_2 measurements for the 3 psi oxygen mixtures showed that with the lower oxygen partial pressure the nitrogen mixture did not cause significant differences from the controls (Figure 13). The Pco_2 for the argon mixture was above normal but considerably lower than that induced by the 35 psi oxygen/130 psi argon mixture. The increase was presumably almost all due now to the high density of this mixture causing respiratory embarrassment.

Ths most significant difference was the considerable fall in Pco_2 with the oxygen-helium mixture. This could explain the increased time to oxygen convulsions with such mixtures[44] and the paraesthesias and other symptoms of hypocapnia described by deep divers at rest breathing oxygen-helium. Once at work these sensations disappear, presumably because the Pco_2 then rises toward more normal levels.

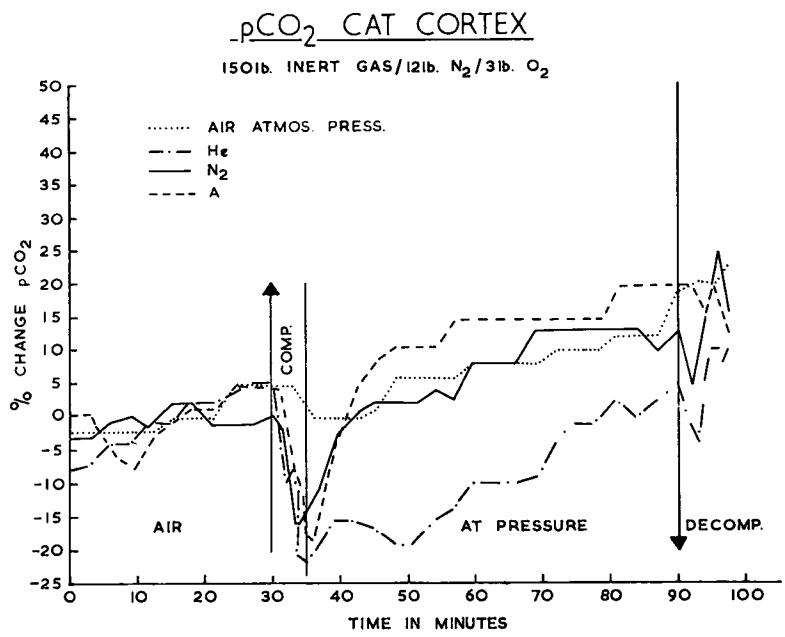

Figure 13. Cat Cortical Carbon Dioxide Tensions at Increased Inert Gas Pressures without an Accompanying Increase in Oxygen Partial Pressure as in Figure 11. Complete decompression results are not given.

From these results it is probable that a high O_2 tension without an accompanying increased CO_2 tension is effective in overcoming inert gas narcosis. If substantiated, this would be further indication of a histotoxic hypoxia as the mechanism of narcosis. Helium, due to its low density, apparently produces such conditions as Schreiner et al[13] found that inhibition of growth rate in Neurospora crassa by inert gases did not occur at high oxygen tensions. Ebert, Hornsey and Howard[11] also support such a hypothesis.

An alternative would be to use assisted ventilation, which besides helping to overcome any respiratory embarrassment caused by the more dense gases, might lower the Pco_2 and raise the aO_2. Buhlmann has stated that such assisted ventilation does in fact prevent inert gas narcosis[38].

From a general consideration of these results, which are to be considered in detail elsewhere, it is apparent that the cause of inert gas narcosis is not due to a high carbon dioxide tension alone, as suggested by Bean, Buhlmann and Seusing and Drube[37,38,39]. In the presence of raised tensions of inert gas, however, CO_2 has a marked synergistic, narcotic action. Further, the increased O_2 partial pressure rather than increased density is primarily responsible for the retained Pco_2 although the latter may well add further to the problem, especially in the very dense mixtures. Whether or not inert gas narcosis occurs, appears therefore to depend on the summated result of three factors. These are an

increased inert gas partial pressure, the oxygen partial pressure and the density of the mixture breathed.

A possible narcotic mechanism for inert gases at increased pressures may be a histotoxic hypoxia, producing a synaptic block by a maintained depolarization, which impairs consciousness by severely depressing the multisynaptic reticular formation of the brain stem and apical dendrites of the cortex.

Current and future experiments at the Royal Naval Physiological Laboratory are designed to further investigate this hypothesis and to clarify the synergistic role of carbon dioxide.

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A THEORY OF INERT GAS NARCOSIS

S. L. Miller
University of California, San Diego
La Jolla, California

INTRODUCTION

In discussing the mechanism of action of inert gas anesthetics, it is necessary to consider only the equilibrium conditions at the site of action of the narcotic agent. The transport and accumulation of these gases in various tissues are important problems and a major part of this symposium, but they do not have any bearing on their mechanism of action.

It is clear that gaseous anesthetics act by some physical process. Xenon is usually taken as the best example of a chemically inert anesthetic. Recently several fluorides of Xenon and one of Krypton have been prepared. These fluorides are prepared from fluorine, and fluorine, as distinguished from Fluoride, does not occur in living organisms. Probably the best argument that gaseous anesthetics do not form covalent or ionic bonds is the large number of compounds with similar or identical anesthetic action. Since these compounds exhibit greatly different chemical reactivities, it is clear that the common denominator must be their physical action.

It is also clear that the mechanism of action of inert anesthetics does not depend on the state of the pure gas at room temperature. Thus nitrogen, which can only be a gas at room temperature, most probably acts by the same mechanism as chloroform, which is a liquid. These liquids are sometimes referred to as volatile anesthetics, but they will be included here with the gaseous anesthetics.

THE MEYER-OVERTON THEORY OF NARCOSIS

The most widely held theory of inert gas narcosis is the Meyer-Overton theory which relates anesthetic action to lipid solubility. This theory, as formulated by Ferguson[1] and Brink and Posternak[2], states that equal anesthetic effects are obtained when equal mole fractions of the anesthetic are present in the lipid parts of the nerve.

The narcotic activity, A_{narc}, is defined as

$$A_{narc} = \frac{f_{narc}}{f^o} \simeq \frac{P_{narc}}{P^o}$$

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where f_{narc} is the fugacity of the anesthetic used, and f^o is the fugacity of the pure liquid anesthetic at the temperature of the experimental animal. For liquids with vapor pressures less than one or two atmospheres, f_{narc} can be replaced by P_{narc}, the partial pressure of the anesthetic, and f^o can be replaced by P^o the vapor pressure of the liquid. For gases such as N_2 and A, which are above their critical points, a pseudo vapor pressure is calculated by extrapolating the vapor pressure curve determined at lower temperatures. If the anesthetic forms an ideal solution in some phase, then the mole fraction, X_2, of the anesthetic is given by the equation

$$X_2 = \frac{f_{narc}}{f^o} .$$

It follows from these two equations that

$$A_{narc} = X_2,$$

or the activity of the anesthetic (relative to the pure liquid) is equal to the mole fraction of the anesthetic in those phases which form an ideal solution. One would expect that anesthetics would form an approximately ideal solution in a lipid. Olive oil is usually used as the model for the lipid phases of a nerve. The solution of these gases in water, however, is very far from ideal.

Figure 1 shows the correlation obtained with the Meyer-Overton theory. The line corresponds to an anesthetic mole fraction of 0.025 for the third plane of the third stage of anesthesia. The correlation can be considered rather good. The greatest deviation is with sulfur hexafluoride. A number of the halogenated hydrocarbons also deviate significantly from the line.

One can apply the results of solution theory to take into account the deviations from ideality of an anesthetic-lipid solution[3]. This would involve the molecular volume, molecular shape and intermolecular forces. Although such corrections can improve the correlation somewhat, such improvement is probably unrealistic in that olive oil is a poor model for the lipid phase of a nerve membrane. This is due not only to differences in chemical composition but also to the thinness ($\sim$100Å) of this membrane.

THE HYDRATE AND ICEBERG THEORIES OF NARCOSIS

It was noticed by Pauling[4] and independently by the writer[5] that a good correlation could be obtained between the pressure for anesthesia and the dissociation pressure of the corresponding gas hydrate at 0° C. This correlation is shown in Figure 2. This correlation is also seen to be rather good. Again the greatest deviation is with sulfur hexafluoride, and the halogenated hydrocarbons are significantly above the line. It can be seen from the figures that the hydrate correlation is about as good as the Meyer-Overton correlation.

It is to be noted that carbon tetrafluoride (CF_4) is absent from these figures. The pressure of this gas to give narcosis has not been determined except that it is above 1 atm[6], if it has any narcotic properties at all. It is also to be noted that the solubility of CF_4 in water is less than half that of helium.

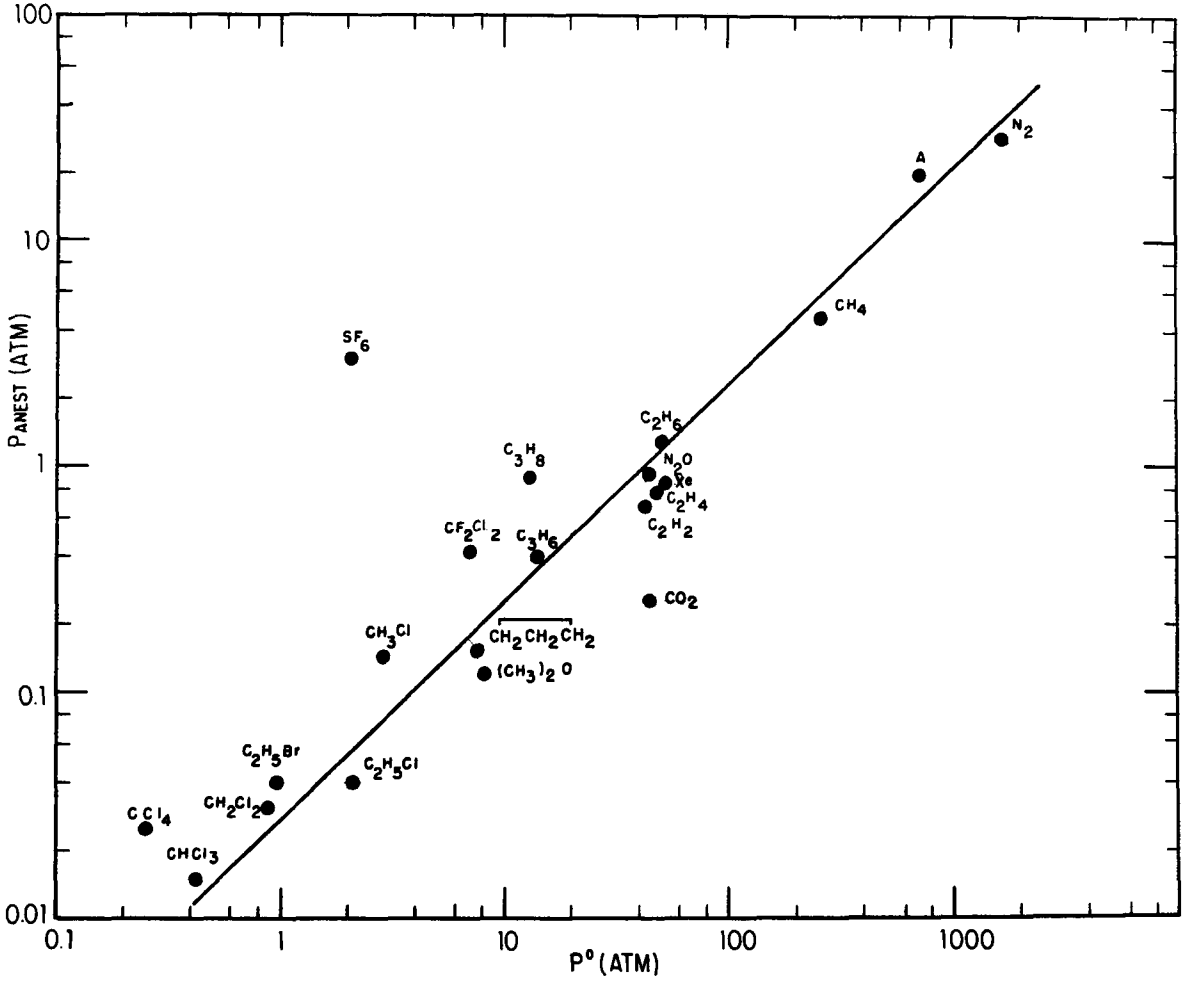

Figure 1. Meyer-Overton Correlation of Anesthetic Pressures with the Liquid Vapor Pressures (or extrapolated vapor pressures). Data from Miller[5].

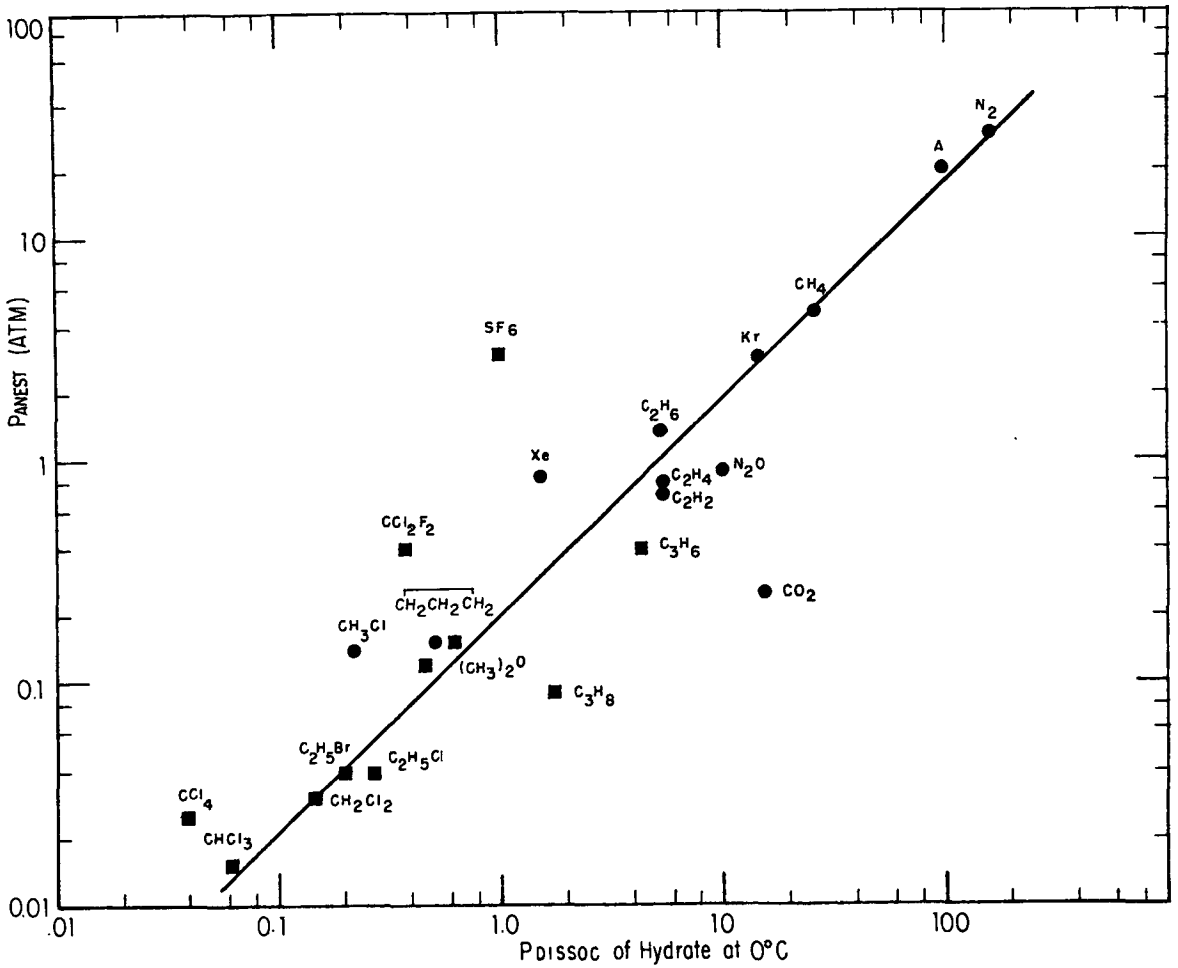

Figure 2. Correlation of Anesthetic Pressures with the Hydrate Dissociation Pressures at 0° C. Structure I hydrates ●; Structure II hydrates . Data from Miller[5].

The gas hydrates. These compounds are not widely known, and it is only recently that their nature and structure have been determined[7,8,9]. They are clathrate compounds, meaning that the gas is held in a cage formed by the host lattice which in the case of gas hydrates is water. The gas hydrates can be considered low pressure forms of ice (there are five forms of high pressure ice known) which are only stable in the presence of the gas molecules in the cages. The gas hydrates are non-stoichiometric compounds, meaning that the ratio of water to gas is not an integer. Thus the formula for methane hydrate is $CH_4 \cdot 6.9\ H_2O$, with the 6.9 not being an approximation for 7. Gas hydrates are known to occur in two forms, Structure I with a 12Å cubic unit cell and Structure II with a 17Å cubic unit cell.

There are 46 molecules in water in the 12Å unit cell of Structure I hydrate, and these waters are arranged to give eight cavities[10]. Two of these cavities are pentagonal dodecahedra, each formed by an array of 20 water molecules. The cavity formed by this pentagonal dodechedra can encage molecules with diameters of 5.1Å or less (N_2O will fit but not CH_3Br). The six larger cavities are tetrakaidecahedra, each formed by an array of 24 water molecules. The cavity formed by this polyhedron can encage molecules with diameters of 5.8Å or less (CH_3Cl will fit but not C_2H_5Cl). This structure is shown in Figure 3.

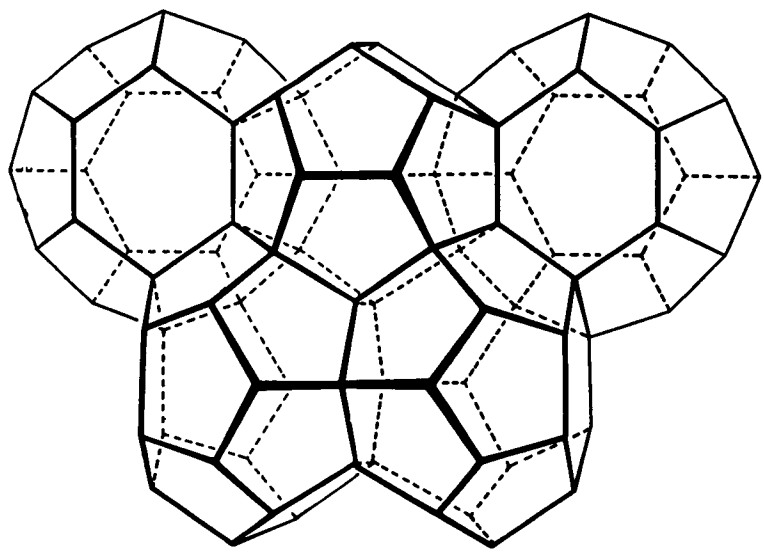

Figure 3. Part of the Unit Cell of Structure I (12Å) Hydrate. The lines correspond to hydrogen bonds, and the corners correspond to oxygen atoms. The pentagonal dodecahedron (upper center) is formed by 20 water molecules. The tetrakaidecahedra (2 hexagonal and 12 pentagonal faces) are formed by 24 water molecules.

There are 136 molecules of water in the 17Å unit cell of Structure II hydrates, and these waters are arranged to give 24 cavities[11,12]. Sixteen of these cavities are pentagonal dodecahedra formed by 20 water molecules. This cavity is similar to the small cavities of the Structure I hydrate but slightly smaller, and it can encage molecules with diameters of 5.0Å or less. The eight larger cavities are hexakaidecahedra, each formed by an array of 28 water molecules. This cavity will encage molecules with diameters of 6.7Å or less (C_2H_5Cl will fit but not n-C_4H_{10}). This hexakaidecahedron is shown in Figure 4.

A number of quaternary ammonium salt hydrates are known. The crystal structures of several of these have been determined recently by Jeffrey and coworkers[13]. These structures are similar to the gas hydrates but have ions instead of gas molecules in the cavities.

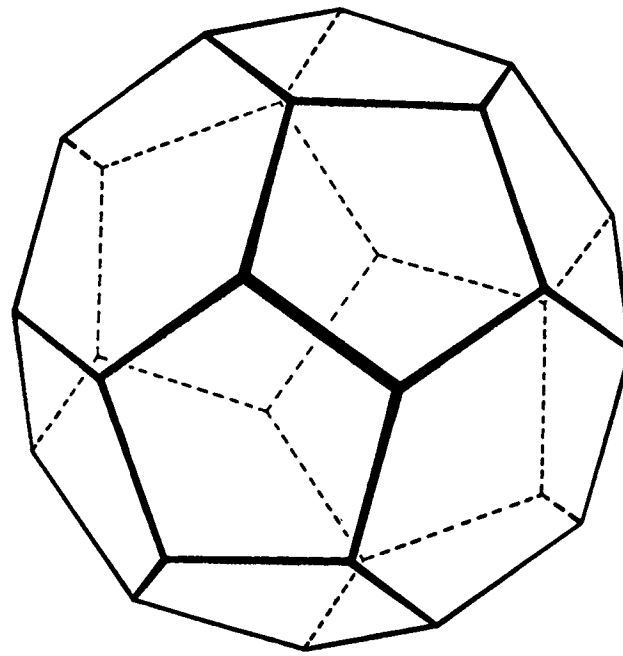

Figure 4. The Large Cavity of the Structure II (17Å) Hydrate. This hexakaidecahedron is formed by 28 water molecules. There are 4 hexagonal and 12 pentagonal faces.

Hydrates and Anesthesia. In considering any connection between hydrates and anesthetics, the first question is whether there are gases which form hydrates but which are not anesthetics. There are a number of such gases: O_2, H_2S, SO_2, Cl_2, Br_2, $CHCl_2F$, C_2H_5F. The dissociation pressures of the hydrates of these gases are 120, 0.95, 0.39, 0.33, 0.06, 0.15, and 2.1 atm, respectively. These gases do not exhibit anesthetic properties since their toxic reactions occur at pressures lower than those probably necessary for narcosis.

The next question would be whether gases with no narcotic properties form hydrates. There are three gases in this class: helium, hydrogen and neon. None of these gases forms a hydrate.

The stability regions of a hydrate can be shown by means of a phase diagram. Figure 5 shows the phase diagram for nitrous oxide hydrate. Below 0° C and at pressures below the line indicated by Ice + Hydrate + $N_2O(g)$, only ice and N_2O gas are present, and no hydrate can be formed. At pressures above this line, all the ice will be converted to hydrate giving a mixture of N_2O hydrate and $N_2O(g)$. Along the line marked Ice + Hydrate + $N_2O(g)$, the three phases are in equilibrium, and this pressure of N_2O is referred to as the dissociation pressure

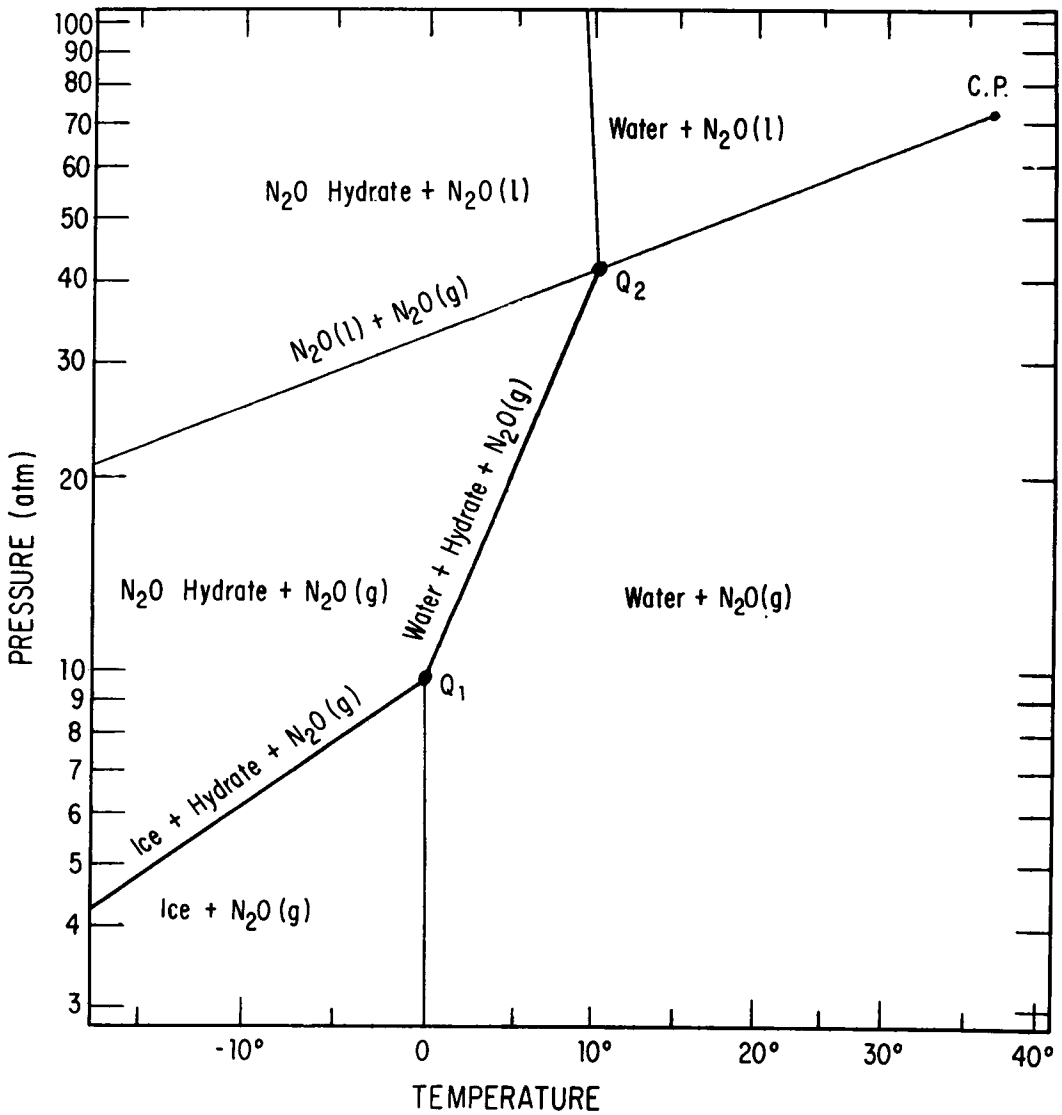

Figure 5. Phase Diagram of Nitrous Oxide Hydrate.

of the hydrate. This pressure depends on temperature, being 10 atm at O°C and 6 atm at -10°C.

The hydrate is also stable above 0° C. At pressures indicated by the line, Water + Hydrate + $N_2O(g)$, the hydrate is in equilibrium with the water and the $N_2O(g)$, the pressure of this gas is the dissociation pressure of the hydrate at that temperature. At pressures below the dissociation pressure, only water and $N_2O(g)$ are present. Above the dissociation pressure, all the water is converted hydrate.

At +10°C the line, Water + Hydrate + $N_2O(g)$, intersects the vapor pressure curve of liquid N_2O, which is the line $N_2O(l)+N_2O(g)$. The vapor pressure curve ends at the critical point of nitrous oxide, 36.5°C. Nitrous oxide hydrate cannot be formed above +10°C because the dissociation pressure of the hydrate is greater than the vapor pressure of the liquid, and the hydrate would therefore decompose into water and liquid N_2O.

If the line, Water + Hydrate + $N_2O(g)$ is extrapolated to 37°, the dissociation pressure would be about 330 atm. Since the anesthetic pressure of N_2O is about 0.90 atm, it is clear that N_2O hydrate cannot be formed from water during anesthesia.

If it is assumed that the correlation of anesthetic potency and hydrate dissociation pressure is more than accidental, then there must be a mechanism by which the hydrates can be made stable at 37°, or the stability of a gas hydrate is a measure of the interactions of this gas in aqueous solution.

Pauling pointed out that small crystals of hydrates, termed microcrystals, might be stabilized by the hydrophobic parts of proteins or other cell constituents[4]. These microcrystals would be of the order of 20 to 30 Å in diameter. The stabilization of this hydrate microcrystal can be understood in the following way. The difficulty in forming a hydrate at 37° is due to the large unfavorable free energy to form the empty hydrate lattice. This instability is approximately that of ordinary ice at 37°. There is considerable ice-like water surrounding the hydrophobic parts of the protein, and the free energy to form an empty hydrate lattice is considerably reduced. When the anesthetic gas is present, the energy gained by putting the gas into the cavities is sufficient to make the microcrystal stable. At temperatures of about 27° there might be sufficient ice-like water present due to the protein side chains to make the hydrate lattice stable in the absence of the anesthetic gas, thereby giving anesthesia by hypothermia.

It would appear that the microcrystals described by Pauling are rather large to be stabilized by the above mechanism, although this is not impossible. There is in any case no experimental evidence available that shows the presence of such microcrystals.

The writer has treated the problem of the instability of the hydrates by showing that the hydrate stabilities are a measure of the interactions of gases in aqueous solution[5]. It is well known that water is an unusual liquid in that it contains a great deal of structure. The amount of this structure is greater at low temperatures than at higher temperatures. The 4° maximum in the density

of the water is due to this increase in structure at lower temperatures. Although there is structure present, the nature of this structure is not known. Most of the theories of the structure of liquid water assume ice-like configurations[14]. Pauling has proposed that liquid water is a Structure I hydrate with the cavities occupied by water molecules instead of gas molecules[15]. A recent model of water based on X-ray evidence indicates that the structural element of liquid water is a distorted ice matrix[15].

A solution of non-polar gas in water has a number of unusual thermodynamic properties, as pointed out by several investigators[17,18]. The solubilities are low, the entropy of solution is large, and the partial molal heat capacity is extremely large. These data have been interpreted to mean that the water surrounding the gas molecule is more highly ordered that the water in bulk solution. This more highly ordered water is sometimes referred to as an "iceberg." This "iceberg" is not a static structure, but is formed and broken down rapidly with a life time as short as 10^{-10} sec. Not all of the gas molecules are surrounded by an "iceberg." Some of the molecules fit into the larger empty spaces or quasi-lattice sites of the liquid water without forming an "iceberg." The fraction of gas molecules surrounded by "icebergs" is high for xenon and low for helium.

The structure and size of these "icebergs" is not known, but it is reasonable to think that most of them are the cavities that occur in the gas hydrates. Figure 6 is a speculative idea of what one of these "icebergs" might be like. The polyhedron is the tetrakaidecahedron of the Structure I hydrate. Instead of its being surrounded by pentagonal dodecahedra, the surrounding water is not "ice-like" but rather is "liquid." At low temperatures this "iceberg" would consist of the complete polyhedron and possibly a second hydration layer. As the temperature is raised this "iceberg" tends to "melt" and some of the waters that make up this tetrakaidecahedron would become less structured or "liquid" water.

When an anesthetic gas disolves in water, we will assume that there are three types of water. The first fraction of water, X_w, consists of liquid water with no ice-like structure. The second fraction of water, X_I, is ice-like water or "iceberg" water. These "icebergs" will be assumed to contain a cavity that can encage a gas molecule, but the cavities are empty in this fraction of water. The third fraction of water, X_A, consists of "icebergs" which have gas molecules in them.

These three fractions of water will be present not only in bulk water but also in the water at the protein or lip-protein surface of a nerve. The equilibria among these water fractions can be expressed by the reactions

$$H_2O_w(\text{"liquid" water}) \rightleftarrows H_2O_I(\text{empty "iceberg"}) \qquad (1)$$

$$H_2O_I(\text{empty "iceberg"}) + G\ (\text{gas}) \rightleftarrows H_2O \cdot G\ (\text{filled "iceberg"}) \qquad (2)$$

It can be shown[5] that the equilibrium for reaction 1 is given by

$$\frac{X_I}{X_w} = \exp\left[-\Delta G/RT\right], \qquad (3)$$

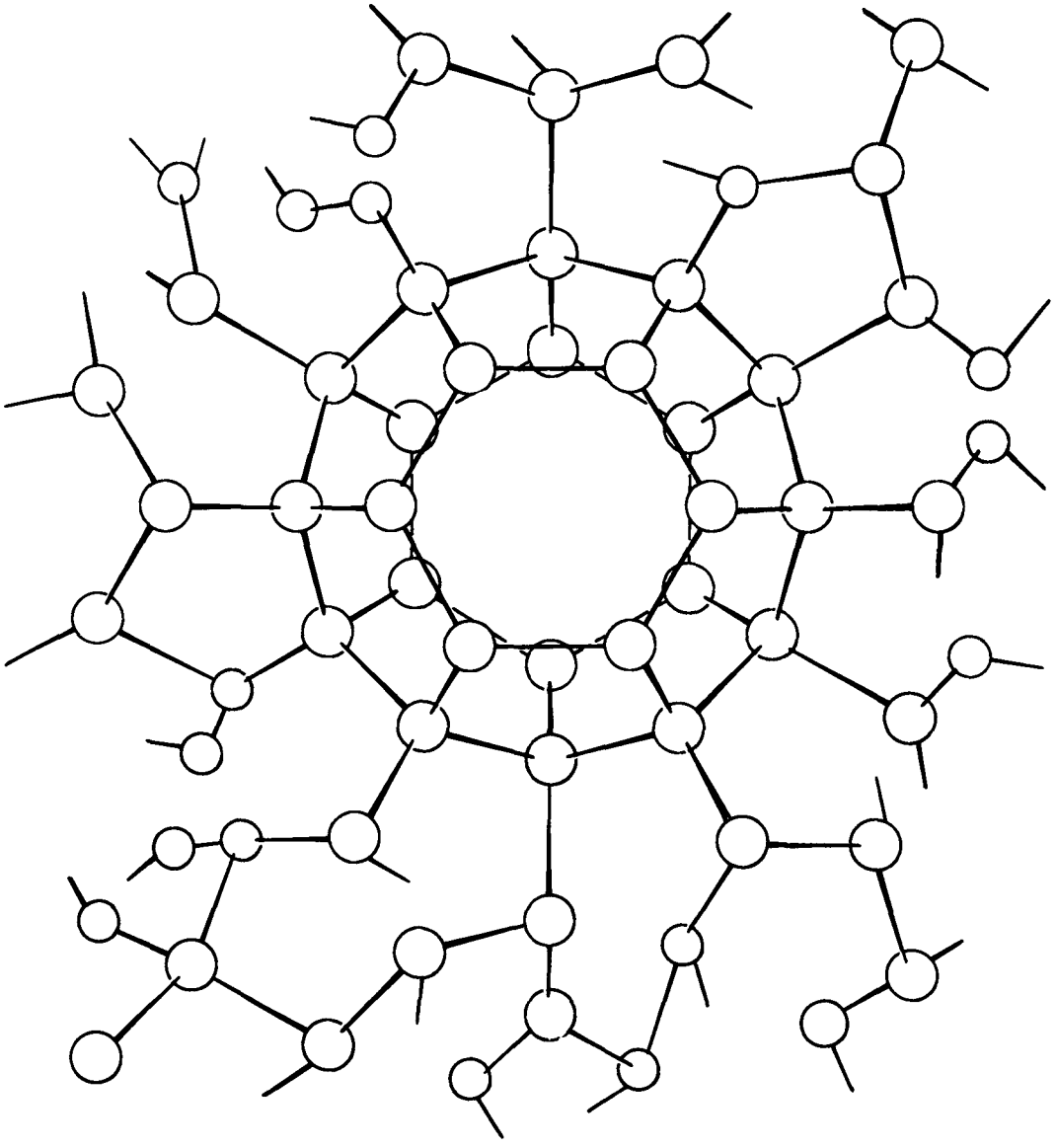

Figure 6. Speculative Model of an "Iceberg." The lines are hydrogen bonds and the circles are oxygen atoms. The polyhedron is the tetrakaidecahedron of the Structure I hydrate. The gas molecule would occupy the cavity. The water outside the polyhedron represents liquid water, the structure of which is not known.

and that the equilibrium for reaction 2 is given by

$$\frac{X_A}{X_w} = P_A \frac{V_f}{RT} \exp\left[(\Delta E - \Delta G)/RT\right] \qquad (4)$$

where ΔG is the free energy of formation of the empty "iceberg" from liquid water, P_A is the pressure of the gas, V_f is the free volume of the gas molecule in the cavity, ΔE is the heat of binding of the gas molecule in the cavity, R is the gas constant, and T is the absolute temperature. Equation 4 can be rearranged to give

$$P_A = \frac{X_A}{X_w} \frac{RT}{V_f} \exp\left[-(\Delta E - \Delta G)/RT\right]. \qquad (4a)$$

This equation states that the fraction of water as "iceberg" at a surface in the different stages of anesthesia, is proportional to the pressure of a given anesthetic. For a given stage of anesthesia, X_A would be the same for all anesthetics, and the pressure of the anesthetics would be proportional to $(RT/V_f) \exp\left[-\Delta E - \Delta G)/RT\right]$. This term is similar to the expression for the stability of the gas hydrate[7,9], except that the values of ΔE and ΔG for the "icebergs" would differ from those for the hydrate. However, the quantity $(\Delta E - \Delta G)$ would be approximately constant for the various sized gas molecules in the different "iceberg" cavities. Therefore, the "iceberg" stabilities would be proportional to the hydrate stabilities, and the correlation of anesthetic pressures at 37° and hydrate stabilities at 0° C can be understood on this basis.

One of the difficulties with the hydrate theories is that many anesthetics do not form hydrates in so far as is known. The most notable of these is diethyl ether. The list also includes hydrocarbons larger than propane, aromatic hydrocarbons, and various ethers. These higher molecular weight anesthetics are too large to fit into the cavities of the Structure I or II hydrates. It is likely, however, that these larger molecules are surrounded by "icebergs" when dissolved in water, since these molecules also have large entropies and partial molal heat capacities of solution. The "icebergs" surrounding these molecules cannot be treated as easily as the gases which form hydrates.

Many hydrogen bonding compounds, such as alcohols, esters, ketones and aldehydes have narcotic properties. The hydrocarbon parts of these molecules would have "icebergs" around them, but the hydrogen bonding parts of the molecule would probably be bonded to the liquid water structure. The estimation of the effect of these molecules is even more difficult to evaluate than for the large non-polar molecules.

The Effect of Temperature on Anesthesia. It would be expected that equal anesthetic effects would be obtained with equal amounts of empty "icebergs" + filled "icebergs" at the sensitive surface. This is to say that

Equal anesthetic effects for equal $\frac{H_2O_I + H_2O \cdot G}{H_2O_W} = \frac{X_I + X_A}{X_W}$

Since the amount of empty "icebergs" increases as the temperature is lowered, less gas filled "icebergs" will be needed for a given anesthetic effect. Therefore, the pressure of anesthetic necessary will be lowered. At sufficiently low temperature (about 25 to 29°) the amount of empty "icebergs" alone is sufficient to result in anesthesia by hypothermia. There are no quantitative data available on the change in pressure of an anesthetic needed as a function of temperature. The temperature range available for investigation with cold blooded animals might permit the evaluation of the various parameters in equation 4.

Mixtures of Anesthetics. If the "icebergs" are independent at the surface where they act, then we would expect that the anesthetic effect of a mixture of gases would be additive. This can be expressed by the equation

$$\frac{P_1}{P_1'} + \frac{P_2}{P_2'} + \ldots = 1 \qquad (5)$$

Where P_1' is the pressure of gas 1 which will produce a given stage of anesthesia when used alone, and P_1 is the partial pressure of gas 1 in the mixture. Thus if 0.16 atm of cyclopropane and 0.80 atm of ethylene give the same degree of surgical anesthesia (3rd plane, 3rd stage), then a mixture of 0.08 atm of cyclopropane and 0.40 atm of ethylene should be equivalent to either one used alone. The additivity of anesthetics would also be expected on the basis of the Meyer-Overton theory, so that a distinction between the two theories cannot be made on this basis. [1]

If the "icebergs" are very large structures, which is not likely, or if Pauling's microcrystals are responsible for the anesthetic effect, then mixtures of anesthetics will not be additive. This synergistic effect would occur when gases which form Structure II hydrates are mixed with gases which form Structure I hydrates. The equilibria involved are complex and will not be discussed here.

Unfortunately, there are no accurate data available describing the pressures needed for mixtures of anesthetics. Such data should be able to distinguish between the microcrystal theory and the "iceberg" or Meyer-Overton theory.

THE MECHANISM OF ACTION OF ANESTHETICS

Anesthetic agents act on both the conduction of impulses along the nerve axon and on the transmission across synapses. The synapses are much more

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[1] The "synergistic" effect of oxygen for "nitrogen narcosis" reported by Dr. C. M. Hesser at this symposium can be understood on the basis of equation 5. Oxygen is about 1.33 times as effective an anesthetic as nitrogen. (The ratio of the hydrate dissociation pressures). Therefore, 8.0 atm of N_2 is equivalent to 6.0 atm of O_2, and 8.0 atm of air gives 1.6/6.0 + 6.4/8.0 = 1.07. Thus 8.0 atm of air is equivalent to 8.0/1.07 = 7.5 atm of N_2.

sensitive to narcotics than the axon. Different synapses have different sensitivities, with the neurons in the brain being the most sensitive.

The difficult problem with the hydrate theories of anesthesia, as well as with any of the other theories, is to explain in detail how nerve transmission and conduction can be blocked by the presence of the anesthetic. Anesthetics block transmission and conduction by raising the threshold for depolarization[19]. The threshold can be raised by increasing the electrical capacitance or the resistance. The capacitance of the nerve membrane might be increased by the "icebergs" since the structured water would tend to push the double layer of ions further from the membrane surface. This occurs at the mercury-aqueous salt interface[20]. The capacitance is not changed by local anesthetics, but this possibility has not been examined with gaseous anesthetics. The resistance of the nerve membrane might also be changed by the "icebergs." The holes or pores in the membrane might be reduced in effective size by the presence of the "icebergs," or the "icebergs" could interact with the lipid-water interface to reduce the size of the holes through which the sodium and potassium ions pass.

It is possible that the anesthetic exerts its effect on the mechanism of permeability change during conduction or transmission. In Nachmansohn's theory this effect would be on acetylcholine esterase, the receptor protein or the storage protein[21]. In the same way the "icebergs" could also affect the binding, hydrolysis and diffusion of neurohumoral transmitters. These effects can be investigated experimentally.

In summary, it can be said that we have a correlation in the hydrate or water theory of narcosis that is as good as the correlation with the Meyer-Overton theory. The hydrate theory describes the molecular biology of the problem more adequately at the present time, but the mechanism of action of gaseous anesthetics is still very unclear. It will not be easy to prove which of these approaches is correct, and a new theory may be needed. However, it is hoped that the ideas here presented will lead to further experimentation so that eventually we will have a really adequate understanding of narcosis.

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FIFTH SESSION
INERT GAS NARCOSIS

F. G. Carpenter, Chairman

DISCUSSION

WOOD: Dr. Hesser, had your subjects reached the plateau level of training when you tested them?

HESSER: They were pretrained before the experiments.

WOOD: Did you measure alveolar Pco_2?

HESSER: No. The subjects breathed from a Douglas bag to avoid breathing carbon dioxide.

CARPENTER: Dr. Bennett, with the preparation involving the rats, where was the stimulation applied to produce withdrawal response?

BENNETT: To the tail by a little copper loop. The current passed from the tail and then through the feet.

CARPENTER: Have you considered the fact that the acetylsalicylic acid you were studying may have acted as an analgesic quite apart from an effect on narcosis?

BENNETT: Yes.

CARPENTER: If you applied a similar stimulus directly to an isolated nerve, a physiological stimulus would go directly into the spinal cord as a monosynaptic reflex. I wonder if by this means you could avoid any possible alteration of receptor mechanisms or of pain threshold?

HARDY: The electric shock technique is only one of several that can be employed for such studies. I think in this case, it would be all right.

LAMBERTSEN: I would certainly like to hear conjecture about how the drugs Dr. Bennett described might have produced the suggested protection against nitrogen narcosis and oxygen toxicity? Why did you choose those particular drugs?

BENNETT: A number of them had already been tried for oxygen poisoning previously and so we retried them.

CARPENTER: Would you discuss the relationship of the ascending reticular formation as it facilitates the passage of an impulse through a monosynaptic reflex? In other words, is your experiment with the rat a complicated model of an effect produced upon a suprasegmental structure? The end result

would yield the depression of a segmental pathway. The ascending activating system, a very diffuse network of neurons, is extremely susceptible to anesthetic agents.

With respect to the oxygen toxicity problem, would it not be worthwhile to use an isolated structure? Of course, I would personally like to have you use isolated nerve, but other structures might be better, so that you could increase the oxygen tension and perhaps overcome the narcotic effect which you demonstrated.

BENNETT: Just before I came away we were using evoked auditory stimuli in the cat. The cats were artificially respired. Instead of the usually marked depression, with oxygen there was no depression.

CARPENTER: What is the behavior of the gas molecule? There is a certain critical number of molecules arranged along the membrane of an excitable structure. Do high gas pressures interfere with the diffusion of oxygen diffusing into the cell?

MACKAY (D): Dr. Bennett, you mentioned scopolamine. What dosage of scopolamine did you use? Was it comparable to what is used in motion sickness?

BENNETT: We used one mg/kg.

BEAN: Dr. Hesser, did I understand you to say that O_2 and N_2 had synergistic actions and that nitrogen narcosis was increased by oxygen at high pressure?

HESSER: With increasing oxygen the performance decreased and even though we don't have any proof, we believe the effects are due to carbon dioxide, i.e., interference with CO_2 elimination from the tissues. The carbon dioxide and nitrogen may have synergistic narcotic effects.

GILLEN: I would like to make one comment about these experiments. Every one is different, the experiments having been done in different places by different people. The fundamental work using electrophysiologic techniques on animals under anesthesia is different from that on unanesthetized humans. There may not necessarily be a relationship between the results obtained at 5 atmospheres and the results obtained at 10 atmospheres. We ought to be careful in interpreting what Dr. Hesser said about an increase in nitrogen narcosis with increasing oxygen pressures. The experiments at 6 atmospheres are not necessarily comparable to ones he did at lower pressures even when the nitrogen partial pressure was the same.

HESSER: The effective pressures of oxygen and nitrogen may be different. Oxygen (high oxygen pressure) has a stimulating effect on respiration but the increase in nitrogen pressure has a suppressing effect. There is a balance between these two different effects. With further increases in pressure, the nitrogen pressure may be more important.

BENNETT: I think the question of where narcosis starts is a hard one to answer because it depends on whether you are using subjective symptoms or objective measurements as an index. Objectively, the abolition of alpha blocking with inert gas has its effect on the central nervous system even at very low pressures.

CARPENTER: It must be remembered that the Meyer-Overton theory proposes that a critical number of molecules exists at any given site, in a lipoid phase, to produce a certain degree of narcosis. This concentration depends upon the solubility of the particular agent (Table I). This was considered in detail at the last symposium[1]. A major problem is that the measurements we have on lipid solubility of gases are not always reliable. It is very difficult to determine the solubility of a gas in a viscous solution, like olive oil. With benzene it is easier. If we calculate the number of molecules of an anethestic agent at the iso-narcotic pressure in benzene, we get a better correlation than with olive oil. The pressure range of the gases, from helium to cyclopropane varies 3500 fold. If we compare the narcotic pressures for helium and cyclopropane, helium is effective only at hundreds of atmospheres of pressure and cyclopropane at hundredths (fraction) of atmospheres. If you multiply the partial pressure of the gases that I studied by their solubility in benzene we observe only a threefold variation in concentration. If we omit helium the variation is only twofold. So clearly, I think the number of molecules in some cellular phase is important, although I certainly agree it is not necessarily a lipid phase. In fact, there is no evidence whatever that the site of action of these narcotics is lipid but all that need be said is that it is non-aqueous. I would like to ask Dr. Miller whether his and Pauling's concepts really exclude the non-aqueous or lipid phase as a site of narcotic action? Are the two theories totally incompatible?

MILLER: I think I said that the correlation of the two theories was about equally good.

CARPENTER: SF_6 does fortunately fit if the benzene solubility is used.

MILLER: There are some substances that lie off the line in any case. If you want a direct approach to the solution theory, substitute molecular size rather than the molecular concentration as Mullins did[2]. As frequently happens, things get worse when you refine your theory. In addition, the theory I described apparently does not require a lipid phase. If one goes to large size molecules or long molecules, like hexane, it may be that one end of the molecule sticks in, even on the hydrate. One end of the hexane might get into the lattice of the lipid and exert its effect by the water. You might get some micelle formation, as in a soap where the molecules line up preferentially. Also, the ordinary lipo-protein or lipo-protein-water interface is very different from what goes on in bulk solution. One really doesn't know what goes on on surfaces.

BEHNKE: Isn't it possible that the reason you can't say there is better correlation with lipid or water is the fact that in a biological system you can't separate the two? In vivo, proteins form lipid-protein-bound water complexes which cannot be separated physically?

TABLE I

Mice

	Olive Oil			Benzene	
	ED_{50}[1]	Solubility	Concentration	Solubility	Concentration[2]
	ATM	cc/cc	mM/L	Mole Fraction	
Helium	163.	.015	107.	$.77 \times 10^{-4}$	12.5×10^{-3}
Nitrogen	18	.067	52.	4.4	8.
Argon	12.6	.14	77.	8.85	11.1
Methane	2.9	.28	43.	20.7	6.0
Sulphur Hexafluoride	1.87	.25	20.	22.	4.1
Krypton	1.8	.43	34.	26.	4.7
Xenon	.51	1.7	38.	84.5	4.9
Nitrous Oxide	.58	1.6	36.	113.	6.6
Ethylene	.47	1.28	26.	124.	5.8
Difluorodichloro-methane	.26	5.1	57.	495.	12.5
Cyclopropane	.045	7.15	36.	935.	4.2
VARIATION	3500 X		5 X		3 X

[1] ED_{50} the partial pressure of a gas required to abolish electroshock seizures in 50 per cent of a group of mice.
[2] ED_{50} x mole fraction of gas dissolved in benzene at 25° C and at 1 atmosphere.

Hildebrand, J. H. and R. L. Scott. Solubility values. In: The solubility of non-electrolytes. 3rd Edition. Reinhold Publ. Corp., New York, 1950; and Carpenter, F. G., Unpublished data.

Referring to the work of Clements and Wilson[3] with lipo-protein films, the lipo-protein film technique was used to simulate the cell membranes. They found that changes in surface tension also correlate with anesthetic effects. These changes do not take place in any kind of system involving just water. The lipid component must be present.

With reference to the ice crystal concept, at 0° we certainly have ice crystals and an effect called "anesthesia," but the question is whether at body temperatures we actually have this form of water structure.

MILLER: It is fair to say that we have structured water of some sort around gas molecules that dissolve in solution. I don't think one can seriously question this. If you go to very high temperatures, say 100° C, then structured water tends to "melt off." At 37° there is a good deal of it left and the hydrate dissociation pressures at 0° are a convenient representation of this structured water. Whether this is the cause of the anesthetic effect is entirely another matter.

With respect to the lipid water surface, Clements in measuring the ice structure has proposed that a clathrate type of structured water exists at the monolayer interface.

FILM

INERT GAS NARCOSIS IN MAN
Narrated by LT M.W. Goodman, MC USN
Experimental Diving Unit

These sequences are filmed extracts from ventilatory and narcosis studies conducted during 1962-1963 at the U.S. Navy Experimental Diving Unit. The subjects are breathing, serially, 80 or 85 per cent helium-oxygen mixtures by mask or from a spirometer mouthpiece, and the compressed-air recompression chamber atmosphere. All exposures are conducted at a pressure of 15 atm abs, or 642 feet of sea water. Partial pressures are, therefore, 12.00-12.75 atm abs of inert gas and 3.00-2.25 atm abs Po_2.

Each subject is seen to function and behave quite normally while respiring the helium-oxygen mixtures. In each of the four illustrated cases, performance deteriorates, and behavior transforms to the bizarre within 20-60 seconds following commencement of air-breathing phases.

Noteworthy is the apparent similarity of the disordered behavioral functioning of these subjects. The schizophrenic-like inappropriate effect is demonstrated by three of the four men, with the remaining subject exhibiting, primarily, a pattern of anger and disgust.

Judging from these observed episodes of hyperbaric narcosis induction and fruition, the clinical description can be summarized as consisting of, at first, progressive deterioration of fine coordinating motor abilities, disappearance of jugement and super-ego functions, followed by rapidly ensuring gross motor

function distortion, depression of the level of consciousness, and, finally, loss of consciousness (and anesthesia). All subjects reported complete amnesia for their air-breathing periods. It is noted that the time span of onset-to-full development of the syndrome is exceeded several-fold by the recovery-phase duration. Neither educational-intellectual attainment, scope of previous diving experience, motivation for the test, nor degree of training for the specific experimental routines appear to significantly modify any of the described narcotic syndrome parameters.

Comparisons of these narcosis examples to induction phases of both general anesthesia and ethanolic intoxication seem to be warranted.

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THERMAL PROTECTION DURING IMMERSION IN COLD WATER

E. L. Beckman
Captain, Medical Corps, U.S. Navy
Naval Medical Research Institute
Bethesda, Maryland

If the popular reports of the long distance swimmers doggedly "crawling" across the English Channel with water termperature at 60° F and stories of frogmen going swimming at the North Pole were interpreted literally, then one might assume that body heat loss is no longer a problem for underwater swimmers. Fortunately, we are all sufficiently biased by our own experiences with cold that any such reports are tempered with some skepticism. In fact, there is still much to be learned about the effects of immersion in cold water upon human physiology and performance.

Extensive research has been carried out in the field of thermal protection during exposure to cold air. However, research into the problems of thermal protection during immersion in cold water has been limited. The difference in the rates of heat loss in air and in water causes significant differences in the physiological effects of exposure to cold air and immersion in water at the same temperature.

It is common knowledge that standing nude in a normally heated room with the air temperature at 72° F does not immediately make one feel cold. However, diving into a swimming pool with the water at the same temperature immediately makes one feel very cold and causes a rapid loss of body heat with a decrease in skin and deep body temperature and the onset of hypothermia. Hypothermia may be considered to be a condition in which the deep tissue or "core" temperature of the body is below the normal physiological range, about 97° F or 36° C, and is the temperature at which malfunctions in normal physiology begin to occur.

There is a good explanation for these observations. Water has a specific heat approximately 1000 times greater than that of air so that each cubic centimeter of water adjacent to the skin can take up a thousand times more heat from the body than a comparable volume of air for a given increase in temperature. In addition, the thermal conductivity of water (or rate of transfer of heat by conduction) is some 25 times greater than that of air. During immersion, body heat is therefore rapidly conducted away from the skin into the adjacent layer of water. The rate at which heat is conducted from the immersed human body is so rapid that heat loss is limited primarily by the rate at which heat is transferred by the blood from the central core of the body to the skin. For this reason, thermal balance of the human body when at rest in water can only be attained if the water temperature is 95-96° F.

The rate of heat loss from the immersed human body is of the utmost importance to people who are immersed for long periods of time, i.e., distance swimmers, skin divers, underwater swimmers, hardhat divers, and survivors from disasters at sea. The danger to swimmers from hypothermia is not generally

recognized. The body cooling which swimmers and divers experience has been considered to be a sign of poor physical condition or weakness and their "esprit de corps" demanded that complaints about the effects of the cold be minimized. Since hypothermic anesthesia has become clinically useful, the effects of hypothermia have been more accurately studied and quantitated. McQueen[1] noted that although the deep body temperature at which given central nervous system changes occur varied with different individuals, in general, when the temperature of a human being subjected to hypothermic anesthesia had decreased to 34° C (94° F) amnesia occurred for the period of cooling below that temperature. The patients likewise became dysarthric, and began to lose contact with their surroundings. Pain was generally appreciated down to about 30° C (86° F) when the ability to recognize relatives or surroundings had also been lost. Voluntary motion was lost at 27° C, as were the pupillary light reflexes and deep tendon and skin reflexes. Virtue[2] corroborated these observations and noticed that between the temperatures of 30° C and 32° C cardiac irregularities occurred, such as atrial fibrillation, ventricular ectopic beats, and ventricular rhythms.

Similar observations have been recorded from the Dachau experiments[3]. Loss of consciousness was reported to occur at 30° to 32° C. Therefore, should a swimmer, either intentionally or through necessity, stay in the water long enough to decrease his deep body temperature to below 34° C he would have little recollection of events that followed and would be incapable of carrying out purposeful actions. His operational usefulness would have ceased, and should his body temperature have decreased to 32° C, it is probable that cardiac irregularities would terminate his operational mission. In addition to these more serious sequellae of heat loss from the body core, the effects of regional heat loss upon the function of the fingers, hands, and arms has been found to be a limiting factor in immersion tolerance. Provins and Clarke[4] have demonstrated that as the fingers, hands and arms cooled below 60° F (15.5° C) their subjects developed an increased reaction time, a decrease in tracking proficiency, a decrease in manual dexterity with a loss of tactile discrimination and kinesthetic sensation, as well as a decrease in muscle strength. In our immersion studies conducted at 50° F, some subjects demonstrated a decrease in grip strength of down to 50 per cent of normal after one hour of immersion. The deep-body cooling rates of our thin, nearly nude subjects were from 6 to 9° F/hr when immersed to neck level in water at 50°to 60° F. At these cooling rates the difference between 60 minutes and 75 minutes of immersion could easily mean the difference between consciousness and unconsciousness. Observations on the respiratory and cardiovascular response to immersion in water have also been reported[5]. A review of the physiological responses of the body which limit the heat loss from immersion in cold water, therefore, seems warranted.

The thermostatic neuroregulatory mechanisms of the human are extremely sensitive to specific local temperatures of receptor structures. The capacities for heating and cooling of the human system are so adequate that changes in deep body temperatures of more than 1° C are rarely experienced by any of us in good health, even though the heat generating systems or heat dissipating systems vary their operating load by a factor of 10. If, in any period, heat production and heat loss from the body are not equal, the difference D, will change the average temperature of the tissues of the body, by the equation:

$$D = M - H = \frac{m\,s}{S} \times \frac{d\theta}{dt}$$

in which M and H are the heat production and heat loss respectively, in kcal/sq m/hr; m is the mass of the body; s its specific heat; S is the surface area of the body; and θ is the mean temperature of the body in ° C. From this equation, the rate of change of the average body temperature will be in ° C per hour[6].

Although theoretically the quantity of heat in the body at any time could be determined from the "mean" body temperature, the mass of the body, and the specific heat, it is practically impossible to obtain an accurate value for θ. As a result, extensive simplifying assumptions are made so as to adjust the theory to experimental data. When experiments are made in air, a mean skin temperature is obtained by a mathematical weighting scheme which has been adjusted to fit experimental data. When experiments are done on body immersion, the simplifying assumption is made that the skin temperature equals the water temperature. Obviously, if the Newtonian concepts of thermal transfer obtain, this assumption is erroneous, and may be responsible for the introduction of considerable error in measurements of thermal conductance of the skin.

Deep body temperature measurements from the rectum, esophagus or tympanic membrane are more reliable than the skin temperature, which varies significantly in different parts of the body, and is lower in the dependent portions of the body, i.e., feet, lower legs and hands, but approximates deep body temperature when measured in the armpit or skinfolds.

It may be assumed for the purpose of analysis, that a man of average weight (70 kilograms or 154 pounds) would have an average specific heat of 0.83[1], even though the specific heat of the human body varies to some extent and is dependent upon the per cent composition of muscle, bone, and adipose tissue. This implies that for a 70 kilogram man, an imbalance in body heat exchange of 58 kilogram calories (kcal) would result in a change in body temperature of 1° C. If a thermal imbalance of the body resulted in a loss of heat of only 232 kcal, the mean body temperature would be decreased from 37° C to 33° C where cerebral dysfunction would occur. When one reflects that this 70 kilogram man at rest generates 70 kcals of heat per hour and that, when vigorously working in a hot or cold environment, he may generate or lose 5 to 10 times this amount of heat in one hour, then the effectiveness of thermal balance in the human body can be appreciated.

Under ordinary conditions the heat loss from the body in air may be formalized with the following equation:

$$H_n = H_c + H_d + H_e + H_r$$

[1]The specific heat of a substance may be defined as the ratio of the thermal capacity of the substance (quantity of heat necessary to produce unit change in temperature in unit mass of the substance) as compared to the thermal capacity of water, at 15° C.

in which H_n is the total heat loss of the body; H_c is the heat lost by convection; H_d is heat lost by conduction; H_e is heat lost by evaporation; and H_r is heat lost by radiation. In considering the problem of thermal balance of the underwater swimmer or of the human immersed in water up to neck level, it is possible to eliminate the terms of H_r and H_c, inasmuch as there are essentially no heat losses by radiation and convection from the body in water.

There is also no evaporation from the skin of the immersed body. H_e or the evaporative heat loss therefore is limited to the amount lost by evaporation from the elveolar surface of the lungs, plus the heat required to warm the inspired air to body temperature, and the heat required to increase the water vapor content of the air up toward 100 per cent. This quantity of heat is lost to the body on expiration. It has been variously estimated by different investigators. Carlson et al[7] used 24 per cent of the total body heat generated as the pulmonary loss. Bribbia et al[8] measured the heat loss of vaporization from the lungs of men exercising in the Arctic to be 9 per cent of the total heat expenditure and also demonstrated that the water vapor loss was proportional to the ventilation rate. These values are in close agreement with Day's approximations for heat of vaporization[9].

The heat required to warm the air used in respiration may be readily calculated if it is assumed that the temperature of the expired air is constant at 37° C. The temperature of the expired air decreases with the drop in the deep body temperature and with increased ventilation rates. Although this assumption is inaccurate, it is sufficient for these calculations:

TABLE I

Heat Lost from the Lungs at Various Air Temperatures* After Day[9]

Air Temperature °C.	Heat Lost to Air kcal	Heat Lost Through Vaporization kcal	Total Heat Lost kcal
37.5	0.00	7.77	7.77
20.0	2.87	12.27	15.14
0.0	6.16	14.78	20.94

*The values are kilocalories per hour, and the assumption is made that the relative humidity is 50 per cent, and the respiratory rate is 600 liters of air per hour.

In our studies on immersion in water at temperatures from 35° C to 10° C and with air temperatures of 20 to 23° C and relative humidity of 40 to 55 per cent, the respiratory minute volumes of our subjects varied from a minimum in warm water of 400 liters per hour to a maximum in cold water of 3000 L/hr. Day used a mean value for respiratory volume of 600 L/hr so that the heat loss from the

lungs of our subjects would have varied from approximately 10 to 100 kcal/hr. The total heat generated by our subjects as determined by oxygen consumption[10] varied from 65 to 600 kcal/hr. The heat loss from the lungs of our subjects would have been approximately 15 per cent of the total heat generated and this is significantly less than the 24 per cent used by Carlson.

The greatest amount of the heat lost during immersion is therefore due to Newtonian cooling, i.e., conduction of heat from the warm body to the cooler surrounding water. The heat loss from the body via conduction may be expressed by this formula:

$$H_d = 5.55 \frac{A(T_c - T_w)}{I_s + I_c}$$

in which H_d is equal to the heat lost to the environment via conduction in kcal/hr; T_c is equal to the core temperature of the body in ° C; T_w is equal to the water temperature in °C; A equals the immersed surface area of the body in square meters; I_s is the thermal insulation of the skin and subcutaneous tissue in CLO^2; I_c is the thermal insulation of the clothing in CLO; and 5.55 is the conversion constant for converting the total insulative value into CLO.

In this equation, the water temperature is assumed to be equal to the temperature of the skin. This is an obvious over-simplification. Upon immersion, the skin temperature rapidly, but asymtotically, approaches but does not equal water temperature so that this approximation is reasonable. Furthermore, since the body "core" temperature T_c, can be limited to the temperature range in which the body function is normal, this term may also be made a constant. The surface area of the human body is constant for any given time, although change in surface area of 5 per cent results from a change in weight of 10 per cent.

The insulation of the external tissues of the body, I_s, is an important variable. The many-fold variations of the insulative covering of the body can be judged by references to Table II which lists values for thermal conductivity of the human body obtained by different investigators on obese and thin men immersed in water at different temperatures. The insulation of the body K_i, in ° C/kcal/sq m/hr is the reciprocal of the thermal conductivity of the tissue, in kcal/sq m/hr/°C.

From this table it is apparent that tissue insulation of humans may vary 15 fold, under different conditions. The lowest thermal conductivity, 2.2 kcal/sq m/hr/°C (highest insulation), was found on an obese, long distance swimmer when his body insultation was measured while he was resting, immersed in a water bath at 10° C. This same individual had a thermal conductivity of 33 kcal/sq m/hr/°C when measured with the subject seated in a bath with a water temperature of 36° C. This difference in conductivity represents the difference of tissue

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[2]CLO is a unit of insulation defined by Gagge, Burton and Bazett[11] which allows the heat transfer of 5.55 kcal/sq m/hr at a temperature gradient of 1° C.

TABLE II

Table Showing Value of Skin and Subcutaneous Tissue Thermal Conductance of Different Humans

Tissue	Thermal Conductivity (kcal/sq m/hr/°C)	Reference
Human (obese) Resting in 10° C water	2.2	Carlson et al[7]
Human (obese) (J. Z.) Resting in 16° C water	5.9	Pugh and Edholm[12]
Human (obese) Resting 33° C water	9.1	Carlson et al[7]
Human (thin) Resting 33° C, 24° C and 20° C water	9.1	Carlson et al[7]
Human (thin) (G. P.) Resting 16° C water (Shivering)	12.7	Pugh and Edholm[12]
Human (obese) (J. Z.) Swimming 16° C water	13.4	Pugh and Edholm[12]
Human (thin) (G. P.) Swimming 16° C water	24.7	Pugh and Edholm[12]
Human (obese) Resting 36° C water	33.0	Carlson et al[7]
Fat in vitro	14.4 per cm thickness	Henriques[13]
Muscle (wet) in vitro	39.6 per cm thickness	Henriques[13]
Water	53.0 per cm thickness	CUSP Report[14]

conductivity with maximum vasodilation (at 36° C) and maximum vasoconstriction at 10° C. Carlson, et al[7] demonstrated the changes in the tissue insulation of this obese swimmer at different immersion temperatures as can be seen on the uppermost line in Figure 1. The thinner subjects showed less temperature effect and the thinnest subject, represented by the bottom line of the graph, showed essentially no change in tissue insulation from 33° C to 20 ° C immersion temperatures. When the tissue insulation was plotted against the specific gravity and per cent obesity of these subjects, there was a linear relationship (Figure 2).

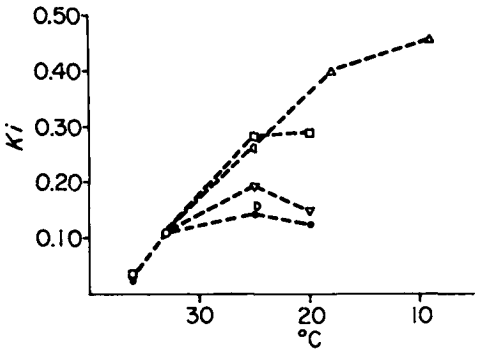

Figure 1. Body Insulation Calculated at Various Water Bath Temperatures. Each symbol is a separate subject. From Carlson et al[7].

These values for "external tissue shell" insulation have all been obtained by inference, i.e., the body oxygen consumption has been obtained and this value equated with equivalent heat generation. A percent of this heat value is assigned to the pulmonary evaporative loss discussed above, and the remainder is assumed to be lost to the water by conduction. Heat exchange from the head is also neglected. As discussed previously the 24 per cent loss may be excessive. Any errors would tend to give high thermal conductivities, but these errors would be consistent so that the determinations are of value for comparison. It is interesting to note that Carlson computed the apparent thickness of the insulative layer of his swimmer using the equivalent conductance of adipose tissue (Table II) and found apparent insulation thicknesses of 73 mm at 10° C, 20 mm at 33° C, and 5 mm at 36° C. The measured skinfold thicknesses of this subject were: arms - 18.5 mm, chest - 18.5 mm and abdomen - 17 mm. This data would not only imply that adipose tissue is an effective insulator but that it is this adipose layer plus a layer of underlying muscle that functions in conserving body heat.

The effective insulation values of the skin and subcutaneous tissue shown in Table II are higher and lower than those generally quoted. Hardy[15] gives the values of thermal conductivity of man as 6 to 9 kcal/hr/sq m/°C and as 5 to 8 kcal/hr/sq m/°C for women. These values represent measurements in air and in a body calorimeter but are in general not obtained under extreme rates of heat exchange such as those in Table II. Our own studies on immersion of subjects to neck level at water temperatures of from 10 to 34° C give values for thermal conductivity more in agreement with those in Table II. The 15 fold variation in effective body insulation, if accurate, suggests an explanation as to why the "fat man" can tolerate cold so much better than the thin man. The effectiveness of adipose tissue as an insulative layer in preventing body heat loss has also been demonstrated by Keatinge[16]. He immersed a group of subjects in 15° C water for 30 minutes and compared their body heat losses, as measured by rectal temperatures, with their adiposity or skinfold thickness. He observed a linear relationship between the amount of body heat lost and the reciprocal of the skinfold thickness, Figure 3.

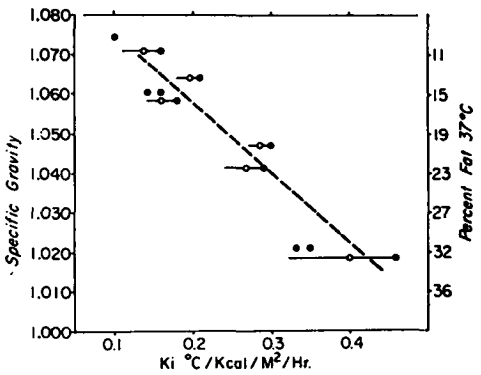

Figure 2. Maximum Values (solid circles) of Body Insulation Found for Various Subjects in the Water Bath. Average of several determinations (open circles). From Carlson et al[7].

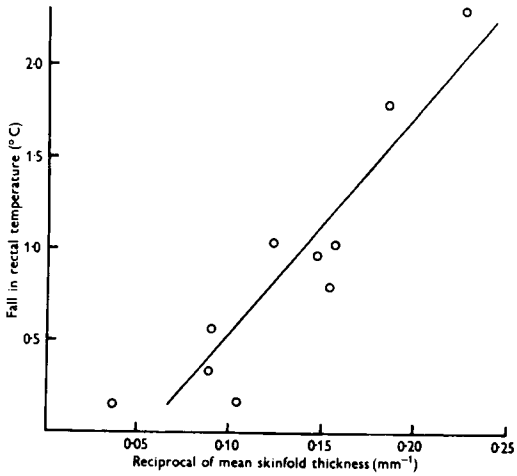

Figure 3. Relationship between Men's Subcutaneous Fat Thickness and their Fall in Rectal Temperature. From Keatinge[16].

The calculation of skin thermal conductivity represents a mean value and implies that tissue conductivity is relatively uniform, and that the vasomotor response of the skin of the body is approximately the same throughout. Froese and Burton[17] measured the heat loss from the human head and observed that the tissue insulation of the human head differs from that of the "mean" body insulation, and is relatively constant at 0.4 CLO when measured at air temperatures between -21 and 32° C. The rate of heat loss from the head therefore increased from 38 kcal/sq m/hr at 32° C to 340 kcal/sq m/hr at -6° C. Such measurements have not been reported on the immersed human head but the Dachau experiments[3] support the thesis that the head is the most critical part of the body in protection against cold water. As an example, in one experiment in which the subject lay horizontal in the water with his neck and the back of his head immersed in water at 54° F, (12° C) the rectal temperature dropped to 70° F (26° C) in 70 minutes. Subjects exposed in this manner were found to have edema of the brain, increased cerebrospinal fluid pressure, and, in some cases, intracerebral hemorrhage. In our experiments, subjects have been immersed in 50° F water up to neck level for 60 to 90 minutes with a drop in rectal temperatures varying from 3 to 5 ° F, which implies that immersion of the head and neck induces a significantly greater heat loss.

The consideration of the "average" insulation of the body has one other disadvantage, in that it disregards the areas of the body where the insulation is anatomically poor, i.e., on all appendages, fingers, hands, toes, ears, nose, feet and male genitalia. The well-known difficulty which is encountered in providing adequate protective clothing for these parts of the body can be explained partly on the basis of poor insulation, and partly on the geometry of the parts. The equation for heat loss given above applies only to insulation on a plane surface. The rate of heat loss from cylindrical and spherical surfaces is also a function of the geometry. This problem received considerable attention during World War II when the operational theaters included the Arctic as well as the minus 55° C ambient temperature realm of the flyer. The theory which relates to the geometry of the heated body is beyond the scope of this paper. A complete analysis of the special problems of heat loss in the hands is given by van Dilla, Day and Siple[18] and should be consulted for details. It is sufficient to point out that because of their geometry, the rate of heat loss from the fingers and other small appendages is so great that these areas of the body frequently limit exposure tolerance to cold when the skin and deep temperatures of the larger body masses are still within the comfort zone.

Thus, it is apparent that there are only two principal physiological processes which limit the rate of heat loss from the immersed body: 1) evaporative losses from the lungs, and 2) conductive losses from the skin. The evaporative losses are relatively constant and directly related to the minute volume of respiration. The conductive losses, which are the more important, are limited by the factors which affect the thermal conductivity of the skin. These are the thickness of the adipose tissue with its regional variations, and the state of the vasculature of the skin which varies from maximum vasodilatation with maximum conductivity, to maximum vasoconstriction with minimum conductivity. The "average" thermal conductivity of the skin may vary 15 fold. When these extremes of conductivity are inadequate to control the rate of heat loss, some additional physiological regulatory mechanisms are utilized.

When mechanisms to prevent heat loss are inadequate the body will attempt to compensate by increased heat production. At immersion temperatures of 35.7° C (96° F), the so-called neutral temperature for baths, the basal metabolic heat production balances the body heat loss and maintains thermal equilibrium without surface vasoconstriction. At immersion temperatures below this, some increase in either heat production or tissue insulation is required. The increase in tissue insulation achieved by vasoconstriction has been shown to be limited, and therefore, must be augmented by an increased heat production, either by shivering which can increase heat production to 5-7 times basal or by purposeful work such as swimming, which can increase it up to 10 times basal. Unfortunately, the length of time that such high energy work can be continued is limited. Even trained long distance swimmers can only maintain a heat output of 275 kcal/sq m/hr[7] to 310-350 kcal/sq m/hr[12] for 10-12 hours. Trained frogmen are expected to be able to maintain a heat output of 200 kcal/sq m/hr[14]. Damage to human tissue occurs below 55° F (13° C) so that local skin temperatures must be kept above this temperature. In the appendages, intrinsic heat production is so minimal that skin temperature can only be maintained by an increase in convective heating produced by local vasodilation. However, the vasodilation of cold is considerably influenced by the general thermal balance of the body. Spealman[19] made direct measurements on the blood flow in the hand at different water bath temperatures and showed a decreased blood flow with decline of water bath temperatures to 50° F (10° C). Below this temperature there was a striking increase in hand blood flow, which was frequently as large as at a water temperature of 95° F. If, except for the hand, the subject was comfortably warm, alternating vasodilation and vasoconstriction occurred ("hunting"). If the subject was chilled, the degree of increased blood flow was reduced. If the subject was uncomfortably warm, the blood flow in the hand remained high even in water at 10° C (50° F). Therefore, it would seem that the general body heat balance must be maintained before the local vasodilation of the fingers can be mobilized to provide heat to the fingers.

Since long distance swimmers have made an effective adaptation to swimming in cold water, it is appropriate to evaluate their particular adaptation. Pugh and Edholm[12] have studied the temperature regulatory mechanisms of channel swimmers. The studies which they did on a channel swimmer and an amateur swimmer are illustrative, not only of the significance of body insulation, but also of the futility of man's plight in cold water. Figure 4 shows the silhouettes of these two subjects. One, J. Z. was short and thick, the other, G. P. was

tall and thin. J. Z. was a professional channel swimmer who had distinguished himself in these races prior to these studies. During the course of this study, J. Z. swam in a 10 mile race in Lake Windermere, England, when the water temperature was 16° C. He had no decrease in deep body temperature (rectal) as seen in Figure 5. However, when he was immersed to neck level in water at 16° C but was not swimming, his deep body temperature was seen to decline, although he did not overtly shiver. Also in Figure 5, the response of the tall thin subject G. P. can be seen under similar circumstances. G. P. 's body temperature dropped precipitously from 37° C to below 34° C when he swam for 30 minutes in Lake Windermere. He began to shiver after swimming for 15 minutes and his muscles became progressively weaker so that he could neither swim nor use his muscles to maintain his body heat. He became incapacitated and had to be helped from the water. This same subject, when placed in a tub of cold water lost body heat at approximately twice the rate of his "thicker" counterpart J. Z. under similar circumstances. In Figure 6, the deep body temperatures of J. Z. following the six hour swim in Lake Windermere are plotted against the depth in the subjects forearm and thigh at which the temperatures were obtained. It can be easily seen that the temperature of the deepest tissue, i. e., muscle, approximates that of the rectal temperature and that the tissue temperatures decrease progressively from the core to the skin. These curves imply that this swimmer not only lost heat from his adipose layer but also from his muscle tissue as well. These temperatures are considerably above water temperature, which undoubtedly reflects the high heat output of the muscles during the activity of swimming. Figure 7 shows the deleterious effects upon the body temperature of the thin individual, G. P., when he swam in cold water. In this graph it is apparent that a man of G. P. 's surface area to mass ratio, and with little subcutaneous fat (less than 5 mm) wasn't even able to maintain his body heat when swimming in water at a temperature of 28. 3° C (83° F).

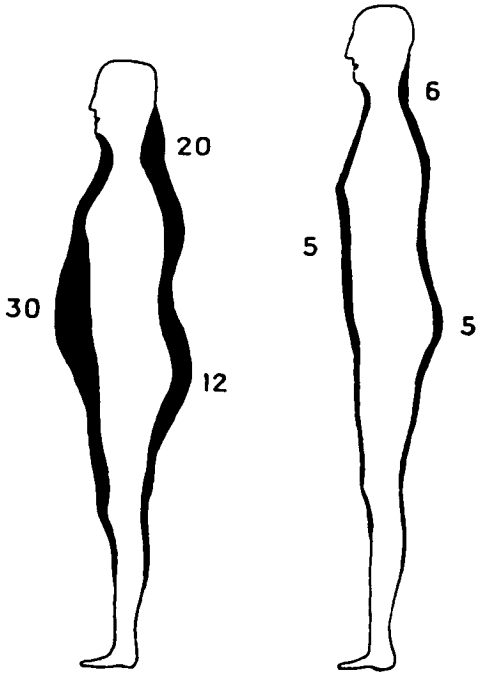

Figure 4. Silhouettes of J. Z. and G. P. Numerals indicate thickness of subcutaneous fat (mm) at the corresponding points. Height of figures is to scale but not thickness of fat. From Pugh and Edholm[12].

The effective thermal conductance and heat productions of these two subjects when swimming in 16° C water and when at rest in a bath at the same temperature are compared in Table III.

It is interesting that both subjects had almost equal metabolic heat outputs while swimming, approximately 600 kcal/hr. However, the layer of adipose tissue which protected J. Z. made the thermal conductivity of his skin and subcutaneous tissue approximately one-half that of his thinner colleague and his tissue insulation twice as effective. As a matter of interest, J. Z. 's effective insulation of .94 CLO would be equivalent to G. P. 's if he were wearing a 1/8" foam wet suit! However, it should not be inferred that J. Z. 's thick layer of body fat provided him with all the necessary insulation required for swimming in cold water, although he thought so. He attempted to swim the Bosphorus when the water temperature was 46° F and swam for four hours. At the end of that time he was semicomatose, had to be taken from the water, and remained in this semicomatose condition for the following three hours. Nor is this the only instance in which channel swimmers succumbed to the cold. Pugh and Edholm reported that the winner of the Ladies Channel Race in 1951 staggered from the water, received congratulations from the judge, and promptly hallucinated about the "furry animals" that had been chasing her on the water! Another channel swimmer was observed to slow his stroke rate markedly and his swimming became almost ineffective. He was taken from the water and it was found that his rectal temperature had dropped to 34° C. He asked for a cotton pledget with which to wipe his eyes and upon receiving it, tried to eat it!

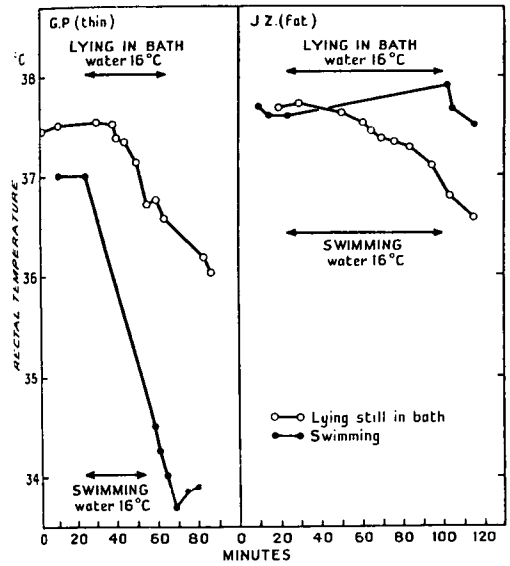

Figure 5. Rectal Temperatures after Swimming and during Immersion without Swimming in Water at 16° C in G. P. (thin) and J. Z. (fat). From Pugh and Edholm[12].

It is important to note that although these channel swimmers were still able to move their limbs in swimming motions, they had lost so much body heat that their brain was no longer functioning normally and they exhibited hallucinations, delusions, and clouding of consciousness. Such insidious cooling of the body, with failure of cerebration preceding failure of locomotion, poses the same type of inherent danger to underwater swimmers that hypoxia does to aviators. These dangers must not be minimized.

From the above considerations it is apparent that hypothermia is a serious problem to swimmers. Moreover, data available to date does not suggest a simple physiological solution to the problem. Increasing the tissue insulation of the body has been proven to be beneficial but this system has limitations too, as determined by the Bosphorus incident. Although a thick layer of adipose tissue is not undesirable for shallow water swimmers (up to 30 foot depth) obesity is currently out of fashion, not only for divers, but for all other service personnel as well.

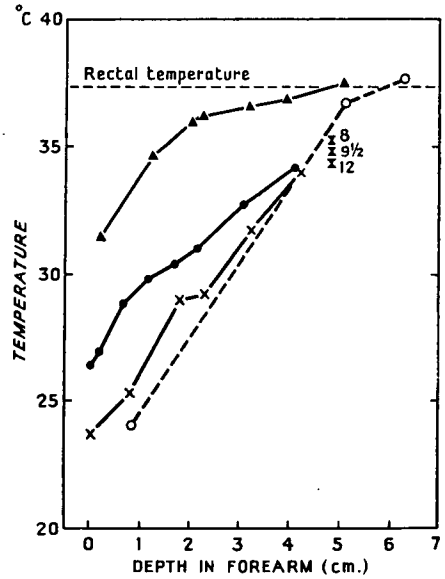

Figure 6. Temperature Gradients in Limbs after Cold Water Exposure. From Pugh and Edholm[12].

x — x in J. Z. 's forearm after long-distance swim of 409 min.

o --- o ditto in thigh.

●——● in J. Z. 's forearm after 60 min immersion without swimming in water at 16° C.

▲——▲ in G. P.'s forearm under normal condition.

⧗ deep forearm temperature at 8, 9 1/2, and 12 min after leaving the water after 63 min swim.

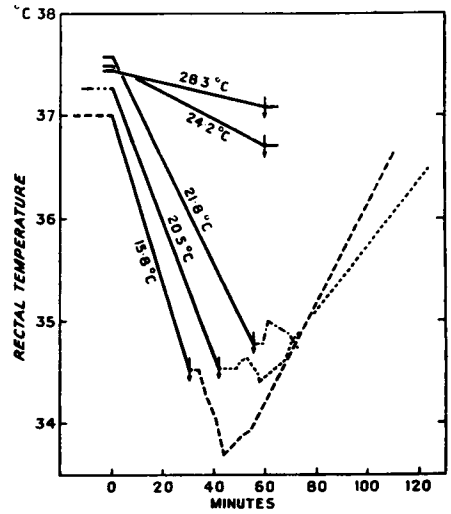

Figure 7. Rectal Temperature in G. P. after Swimming in Water at Various Temperatures. From Pugh and Edholm[12]. Subject entered water at time O; arrows indicate time of leaving water. The water temperatures are shown above the corresponding rectal temperatures.

Increasing the heat production is the other solution. Although it is possible to increase the muscle mass and efficiency of function by training, the possible improvement in heat production is only of the order of two fold whereas the heat loss is five to eight times normal. The most effective method for maintaining body temperature in underwater swimmers is based upon preventing heat loss by providing external thermal insulation around the body. The relative values of different insulating materials are listed in Table IV.

The problem of providing adequate thermal protection for underwater swimmers does not have a simple solution. The first significant break through in this area resulted from the proposal by Spealman[20] some 10 years ago that a foamed neoprene wet suit would be useful. This unicellular foamed neoprene wet suit for underwater swimming has exceeded its original design specifications and has almost completely eliminated the dry suit for free underwater swimming. The 1/4" wet suit was originally designed to provide sufficient insulation for an underwater swimmer in 32° F water generating 200 kcal/sq m/hr to maintain a skin temperature of 58° F and a normal deep body temperature for one hour. A 3/16" wet suit was designed to provide similar thermal protection in 10° C water.

TABLE III

Effective Thermal Conductance and Insulation
From Pugh and Edholm[12]

	Subject JZ (2.0 sq m)		Subject GP (1.9 sq m)	
	Swimming	Bath	Swimming	Bath
Metabolism (kcal/min)	660	270	630	498+30.8*
Heat dissipated through tissues (kcal/sq m/hr)	290.5	118.8	291.6	261.3
Temperatures				
Skin (°C)	16.0	17.0	25.3	16.0
(°F)	60.8	62.6	77.5	60.8
Rectal (°C)	37.4	37.1	37.1	36.6
(°F)	99.3	98.8	98.8	97.9
Difference (°C)	21.4	20.1	11.8	20.6
(°F)	39.5	36.2	21.3	37.1
Conductance (kcal/°C/sq m/hr)	13.4	5.9	24.7	12.7
Insulation (CLO)**	.42	.94	.23	.44

*Stored heat loss.

**Values for CLO in this table are corrected for error in placement of decimal point in values given in original article.

Field tests of a 1/8" neoprene suit demonstrated the effectiveness of the 1/8" foam suit in protecting swimmers in 50-55 ° F water from significant hypothermia for periods up to 45 minutes[14]. Mazzone[21] carried out field trails of the 3/16" thick, double faced, unicellular foam neoprene suit and demonstrated satisfactory thermal insulation in 56° F water for two hours. Tests of this suit in a dry chamber with an air temperature of -20° F and a wind velocity of four knots demonstrated that 60 minutes was the limit of useful activity under these conditions. This suit had an effective buoyancy at the surface of 15 pounds while at 100 foot depths the effective buoyancy decreased to two pounds.

Additional field tests of a 3/16" unicellular, neoprene, wet suit, a 1/4" unicellular, neoprene wet suit, and the Pirelli type dry suit worn over a 1/4" neoprene, wet suit are reported by Martorano[22]. In these tests, the subjects remained essentially motionless while immersed up to neck level in water of 35.4° to 37.8° for periods up to 30 minutes. Temperature measurements were made on the skin of the upper arm, over the back of the scapula, on the chest, on the lateral aspect of the thigh, on the tip of the index finger, and on the great toe.

TABLE IV

Thermal Conductivity of Various Materials

Material	Thermal Conductivity (kcal/sq m/hr/°C per cm thickness)	Reference
Still air	2.3	14
Wool clothing (normal)	8	14
Wool clothing (maximum)	3.4	14
Foamed neoprene*	4.6	14
Solid neoprene or rubber	16	14
Rubber impregnated cloth	16	14
Body, fat	14.4	13
Muscle (wet)	39.6	13
Water	53	14

*Calculated on basis of additive conductivity of neoprene and nitrogen gas. Density of neoprene taken as 1/8 gm/cu cm 0.156 normal density.

Core temperatures were determined by rectal temperature measurement. In these tests the critical skin temperature for cooling of the hands was set at 55° F since the skin of the fingers became numb and sensation of touch and pain were lost with increasing muscle weakness below this temperature. As can be seen in Figure 8, the skin temperature of the fingers decreased to critical values in one-half hour when subjects were wearing the 3/16" wet suit and in one hour when wearing the thicker 1/4" suit. The addition of a dry suit over the wet suit did not significantly decrease the rate of cooling.

The difficulty of providing adequate insulative covering to the hands, feet, and fingers was emphasized in Arctic field clothing research in World War II. Some of the findings of these investigations are described[18,23]. The geometrical dilemma of finger clothing is graphically shown in Figure 9, in which the effectiveness of insulative materials in CLO units is shown for plane surfaces, cylinders, and spheres. This graph shows why it has been said that to provide 4 CLO insulation for the fingers, the fabric thickness would have to be 3.5 inches. This graph also shows that no practical glove insulation can be constructed greater than 1 to 1.2 CLO. This would be approximately the CLO value of a foamed neoprene glove 1 cm in thickness. The result of research and field experience on Arctic clothing reported from the U.S. Army Climatic Research Laboratory is quoted by van

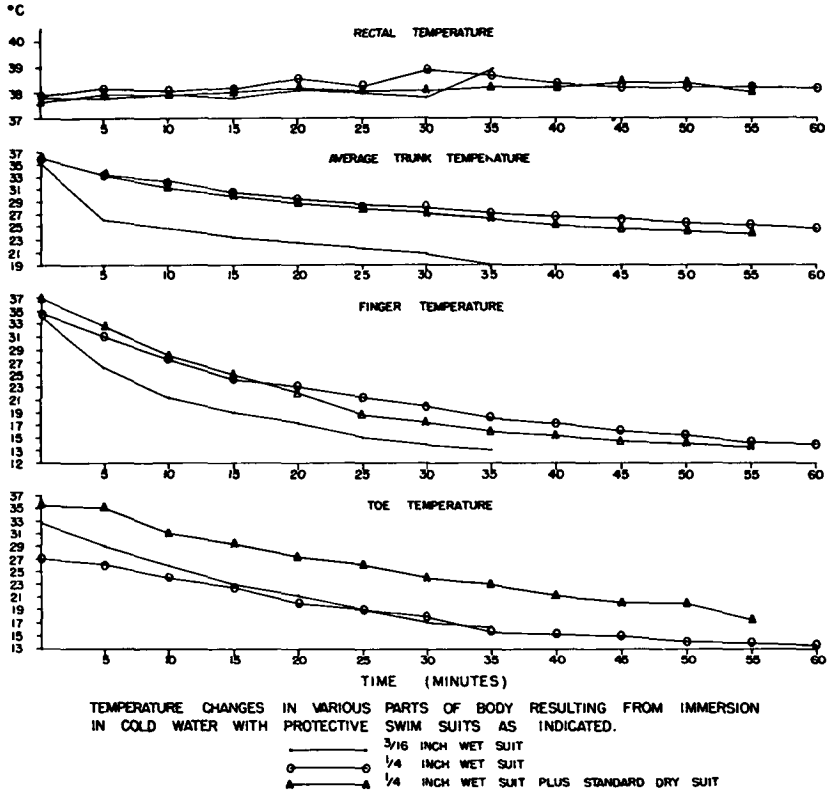

Figure 8. Temperature Changes in Various Parts of the Body Resulting from Immersion in Cold Water with Protective Swim Suits.

Dilla[18] as follows: "The hands cannot be kept warm in Arctic environments except by maintaining a rapid circulation of blood (by exercise), by withdrawing the hand and arm into a parka type shirt or by artificial heat." These same observations are applicable to hypothermia from water immersion as well.

The unicellular neoprene wet suit therefore would seem to have some limitations, despite its many advantages. These disadvantages were to be expected. The original calculations on the development of the wet suit were based upon a desired skin temperature of 58° C. The "comfortable" skin temperature has been demonstrated to be 34-35° C[24]. Somewhat lower skin temperatures are comfortable during exercise in water. Indoor swimming pool temperatures are generally kept at 80° or slightly above for optimal competitive swimming. Rarely are temperatures as low as 74° F used. Consequently, since the purpose of insulative clothing for swimmers is to maintain optimal function, the heavy foam wet suit should be designed to permit a comfortable skin temperature (80-84° F) when swimming in water at 28° F, the freezing point of sea water. To provide such protection, the wet suit would have to have a mean thickness of

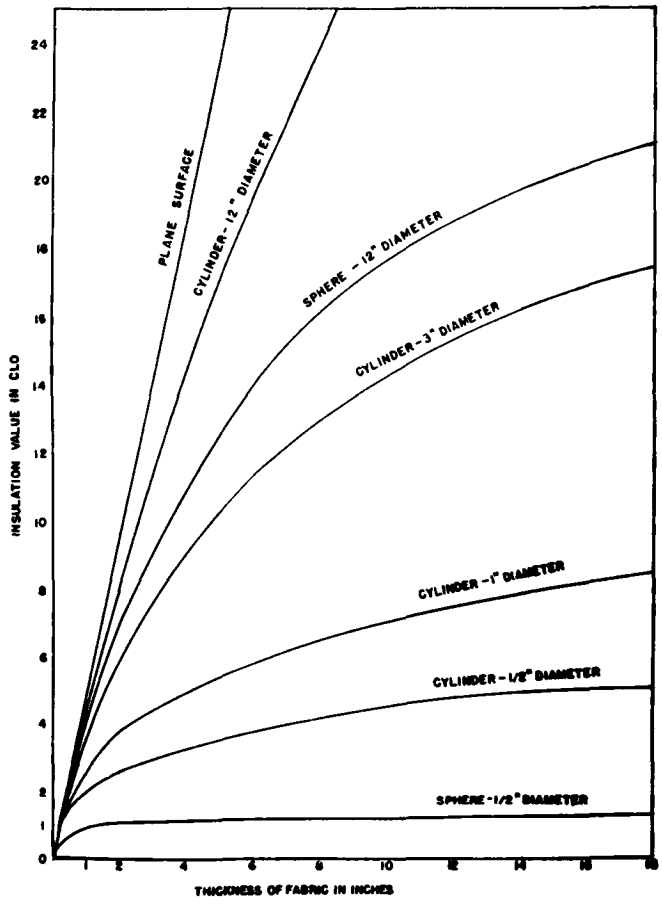

Figure 9. Insulation of Ideal Fabric on a Plane, Cylinders and Spheres. From van Dilla, et al[18].

approximately 0.5 inches or twice the thickness of present heavy wet suits. Even this thickness of foamed neoprene would not provide adequate insulation for the hands for work in 28° F water.

A 1/2" wet suit could, of course, be fabricated, and SCUBA divers have been known to wear two 1/4" foam wet suits in an attempt to retain body heat. However, a suit of this thickness becomes too bulky to wear. In addition, the original calculations for the wet suit stipulated a heat supply from the body of not less than 200 kcal/sq m/hr. This would be a total heat output of 380 kcal/hr for the average 70 kg man. This would be approximately the oxygen consumption found by Hoff, et al[25] to be utilized for maintaining a pace of 1 knot for one hour when swimming with fins. Maintaining this work output for 2, 3 and 4 hours would become progressively more difficult, so that the heat generated by the body would decline with each succeeding hour and the body temperature would also fall. The exact heat deficit which any given swimmer would develop cannot be predicted accurately. In general, it would be expected to be between 100 and 200 kcal per hour and would increase gradually during the period of hypothermia if the muscle mass was cooled and decreased its heat output. An average heat debt of 200 kcal/hr for extremes of water temperature must therefore be expected.

Even though a 1/2" wet suit would satisfactorily insulate the cold-water swimmer operating at a 10 to 15 foot depth, its buoyancy would present a problem if the diver were to change depths. The greatest part of the insulation provided by foamed neoprene is based upon its trapped air. The volume of this trapped air, and therefore the buoyancy and the insulation of the suit, are inversely proportional to the water pressure. The thickness of unicellular, foam, neoprene, wet suits was found to decrease as the pressure increases (Figure 10). Tests of a 1/8" wet suit gave a buoyancy of nine pounds on the surface and six pounds at 35 feet. An average swimmer, using a 3/16" wet suit, required 18 pounds of lead weights for ballast on the surface and the same swimmer using a 1/4" unicellular foam

wet suit required 28 pounds. The change in buoyancy which occurs when an underwater swimmer wearing a foam, neoprene wet suit changes his swimming depth is shown in Figure 11. This decrease in insulation and buoyancy with depth is undesirable, and limits the usefulness of the wet suit for diving at depths. The foamed neoprene wet suit concept of thermal protection for underwater swimming has greatly increased the cold water tolerance time but it still has some deficiencies.

Present developments in diving equipment suggest that divers and underwater swimmers will have available greatly increased bottom times. The development of improved gas mixtures will likewise increase the operating depths of divers. Improved systems of protecting divers from general and localized hypothermia for long periods of time without buoyancy penalties are therefore required. The requirement exists to provide a system to supplement the heat output of the underwater swimmer wearing a wet suit under the following conditions: 1) whenever he stops swimming or working; 2) whenever he swims to greater depths; 3) whenever he must stay submerged for longer than one hour; and 4) whenever maximum manual dexterity is required or whenever cooling of his hands and fingers limits the operational mission.

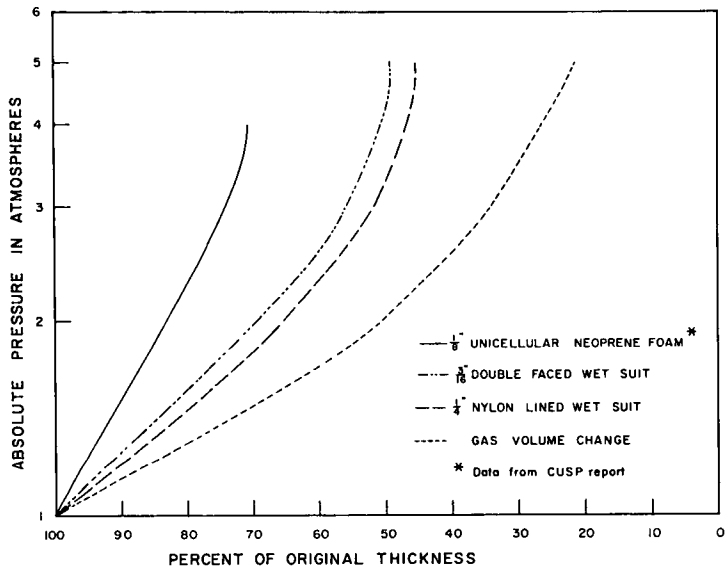

Figure 10. Per Cent Change in Thickness of Unicellular Foam Rubber Swim Suit with Depth.

In order to support a swimmer for a 4 to 6 hour dive in 28 to 40° F water it will be necessary to provide him with approximately 200 kcal/hr additional for 4 to 6 hours. It is anticipated that this external heat source could be readily provided by the use of a resistance wire, thermal suit to be worn under the foamed wet suit or incorporated within its thickness. The present state of the art of battery power suggests that rechargeable batteries could be used which would provide the necessary power to a resistance type thermal suit so as to provide approximately 1 kilowatt hour. Inasmuch as underwater swimmers must wear approximately 15 to 28 pounds of lead weight to compensate for the buoyancy of the foam rubber suit, it would seem logical to replace this inert ballast with a similar weight of electric batteries which could serve both as ballast and a source of electric power. Preliminary calculations on the feasibility of such a suit and preliminary measurements indicate that both the heat requirements and the weight

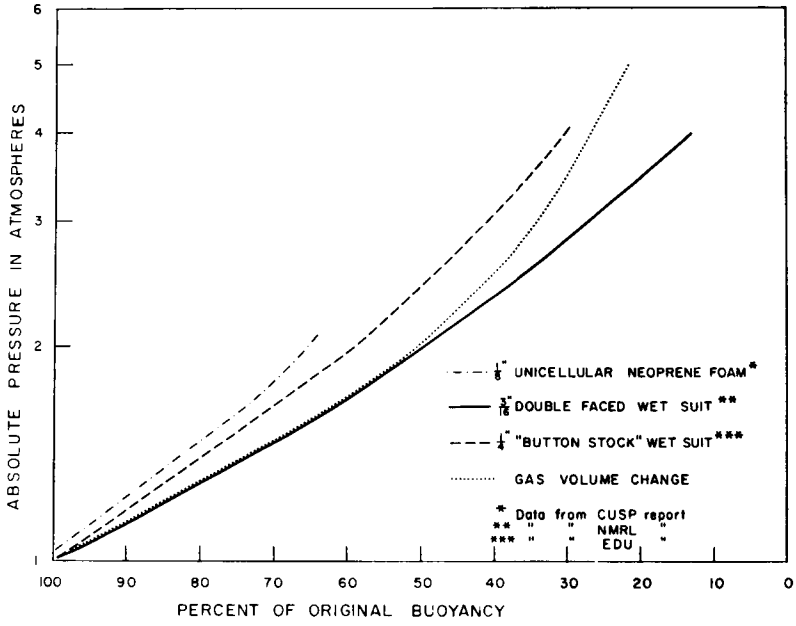

Figure 11. Per cent Change in Buoyancy of Unicellular Foam Rubber Swim Suit (including boots, hood and gloves) with Depth.

limitations can be met by an electrically heated suit, powered by rechargeable (silver-zinc) batteries.

In addition to providing a supplemental heat source for maintaining the mean temperature of the skin and deep tissues, an electrical system could also provide differential heating to the hands, feet and the head. Such a system for providing supplemental heat to the hands is particularly needed and could be under the control of the swimmer. Likewise, the pulmonary heat loss due to evaporation from the lungs and to heating of the inspired air (15-24 per cent of heat production) can be prevented by warming and humidifying the inspiratory air supply. This is technically feasible and would be physiologically beneficial.

In addition to the electric resistance wire system for supplying heat, exothermic chemical or physical processes could undoubtedly be developed which would supply the requisite amount of heat as well.

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CARDIOVASCULAR PERFORMANCE UNDER WATER

L. H. Peterson
Department of Physiology
University of Pennsylvania
Schools of Medicine
Philadelphia, Pennsylvania

This author is uniquely qualified to speculate upon the effects of submersion upon the cardiovascular system since he has had no experience in this field and since there are only a few published reports on the subject. This unencumbered approach can certainly claim to be fresh if not informed. I have, however, engaged in the exercise of matching the sparse available data with considerations of what might be expected to occur. Therefore, I will herein attempt to summarize available information, pose questions and provoke discussion.

Many more observations have been made upon diving animals than upon man. In general, certain behavior patterns emerge from studies of diving reptiles, birds and mammals. These animals are able to sustain themselves under water, and even very deep water, for prolonged periods by reducing their over-all metabolism by a process described by Anderson[1] as "making themselves into smaller animals." Apparently, the blood flow to large muscle and skin areas is markedly reduced[2,3,4,5]. Secondly, nature has provided them with a somewhat larger relative oxygen storage, since their relative blood volumes, myoglobin content and lung volume apparently exceed those of man[1,5].

The evidences for the redistributed blood flow and attendant metabolic changes are: 1) incisions into skin and muscles do not bleed, 2) elevated lactic acid appears in the blood after ascent, suggesting that it is trapped and non-circulating during the dive, 3) the myoglobin oxygen is almost exhausted while blood is almost 50 per cent saturated, 4) direct arterial tracings indicate increased peripheral resistance, i.e., the rate of fall of pressure during diastole is reduced and, 5) "hot wire" techniques applied to muscle indicate a reduced circulation.

Most observations of diving animals show that they gradually develop a marked bradycardia which, in most cases, is of sinus origin, i.e., the electrocardiograph exhibits normal sinus rhythm although arrhythmias do occur[1,5,6]. The pulse rate may decrease to 10 per cent to 50 per cent of the surface rate and the bradycardia, once developed, persists during physical activity and struggle.

These findings of bradycardia and shifting blood flow, together with hypoxia and hypercapnia, indicate that submergence, even in so-called diving animals, has pronounced effects upon the cardiovascular system. There is at least some evidence that similar changes occur in man although man cannot remain submerged for such extended periods. Recent studies of pearl divers of the Thursday Island areas have shown that all but one exhibited bradycardia[5]. Measurements of blood pressure were attempted and, in spite of the difficulties encountered, it was suggested that systolic pressures remained at or near normal levels. Also, lactic acid release into the circulatory blood was delayed until ascent occurred. It has been argued that the lactic acid appearance delay is

difficult to interpret since there is also a delay following surface swimming and sprinting and since man's submergence time is relatively short.

It has been suggested that bradycardia is a "normal" response to asphyxia and it has been recalled that fetal bradycardia is a clinical sign of intrauterine asphyxial distress[5]. Bradycardia does occur in most animals with asphyxia, however, it is my impression that usually it occurs in the severe terminal stages of asphyxia. This author does not know of any specific studies relating asphyxia and bradycardia. It has also been suggested that the shunting of blood away from skeletal muscle occurs because the muscles are in spasm[5].

While it is known that blood flow through contracted muscle is reduced and while severe asphyxia is usually associated with bradycardia there are many other factors associated with diving which are known to affect the cardiovascular system. I would like to mention a few of these and consider how they might relate to or contribute to the shunted circulation and to the bradycardia.

Cardiovascular functions are also affected by altered pressures and/or volumes within the vascular system. Passively raising the legs of supine subjects causes reflex changes in skeletal muscle blood flow[7]. Tilting to the upright position causes reflex vasodilation in skeletal muscle[8].

In the light of the foregoing observations, it is quite likely that conditions underwater will result in many effects upon and within the cardiovascular system. There are several possible causes of blood pressure, pressure gradient and volume alterations. For example, the effects of increased pressure of the surrounding water, the fact that these external pressures may not be distributed equally due to position or even differences in the mechanical structures of the body, and the fact that respiratory patterns may vary (e.g., straining, Valsalva maneuver, forced inspiration with closed glottis, etc.) may all act to cause shifts in blood volume and pressures. It has been shown, for example, that enough blood may be shifted into the thorax to cause pulmonary edema and rales when persons are subjected to increased "g" forces on a human centrifuge if, at the same time, the pressure surrounding the body (including the thorax) is increased. Thus, a "full-pressure" suit which surrounds the limbs, abdomen and thorax is inflated and apparently the relative rigidity of the thorax is such that pressure differentials are established and blood is forced into the thorax. If forced inspiration or expiration efforts are made with a closed glottis very large abnormal gradients may be established. Furthermore, the combined effects of hypercapnia and hypoxia may cause additional changes in the blood vessels and heart. Also, the position of the body with respect to gravity and of one part of the body with respect to another is frequently altered in diving and submerged swimming. The cardiovascular system is also subject to reflex and direct effects of ambient temperature changes.

Of course, the extent to which these multiple factors, individually or collectively, affect the cardiovascular system can now be only speculative. The importance of man being able to function underwater and the possibility that such effects as noted above might occur make it most desirable to substitute investigation for speculation. It is certain that our information presently only indicates

that significant alterations in cardiovascular behavior do occur but is too meager to clarify the responsible mechanisms.

The few reported observations of diving man indicate that the human cardiovascular response is similar to diving animals although man cannot remain submerged without assistance for the prolonged periods characteristic of diving animals. Most men exhibit bradycardia and evidence suggestive of increased vascular peripheral resistance and reduced muscle blood flow. It has been suggested that the bradycardia is due to asphyxia and the reduced muscle blood flow due to muscle spasm. In addition to these possible influences there are many other possible effects of diving on the cardiovascular system. Abnormal pressure gradients may be exaggerated by unusual respiratory efforts or patterns with closed glottis or altered airway resistance. Unusual posture and temperature variations may also contribute to the cardiovascular patterns of diving. The need for further study of diving man is emphasized.

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EFFECT OF PROLONGED DIVING TRAINING

Karl E. Schaefer
U. S. Naval Medical Research Laboratory
New London, Connecticut

The effect of prolonged training in skin diving (breath-hold dives), SCUBA and deep sea diving are related to the particular changes in mechanics of breathing and pulmonary gas exchange observed during diving. These alterations lead, under all three conditions, to some measure of CO_2 adaptation. This paper reviews data on pulmonary gas exchange during breath-hold dives and evidence of CO_2 adaptation as a consequence of diving.

In previous investigations by Bond and Schaefer[1,2,3], alveolar gas samples were obtained from divers at the surface, at 90-foot depth, and again after their return to the surface of the Escape Training Tank. Results showed that a considerable amount of the pre-dive CO_2 content in the lungs had disappeared during descent to 90 feet, thus indicating a transfer of CO_2 from the lungs to the blood. On the basis of theoretical equations, DuBois[4] had predicted such results in pulmonary gas exchange during diving. They were subsequently confirmed in simulated breath-hold dives in dogs[5] and recently in men[6]. In further investigations more detailed data were collected on alveolar pathways during breath-hold dives which produced direct evidence of the existence of a reversed CO_2 gradient[7].

Experiments, reported elsewhere[7], were carried out with an experienced diver who was well trained as a subject in respiratory experiments and whose total lung volume and its subdivisions had been determined repeatedly. Prior to an experimental descent, the diver exhaled to residual volume and then inhaled four liters of normal air from a spirometer. After descending to a predetermined stopping point, he exhaled under water the major part of his expiratory volume through a mouth-piece into bag number 1 used for the collection of mixed expired air; he then immediately exhaled the remainder into bag number 2 used to collect "alveolar air." (The latter usually received 10 to 20 per cent of the total expiratory volume.) The diver then took a breath of air in the diving bell and brought the bags to the surface. This routine was repeated at different depths. Gas samples from the bags were collected in mercury tonometers and the total expired air volumes in the bags was measured. Gas analysis was carried out in duplicate with a Scholander 0.5 cc gas analysis apparatus. The CO_2 and O_2 content (STPD) in the lungs at various depths was calculated from the measured gas tensions and volumes of mixed expired and alveolar air, the predicted volume of residual air, and the calculated total dry gas pressure in the lungs.

Results plotted in an O_2-CO_2 diagram illustrate the alveolar pathways during natural breath-hold dives to a 90-foot depth (Figure 1). The individual points of the solid and dotted curves represent mean values of 3 to 6 measurements of alveolar and mixed expired gas tensions respectively. One dive was required for each of the gas samples collected at the eight different depths. The

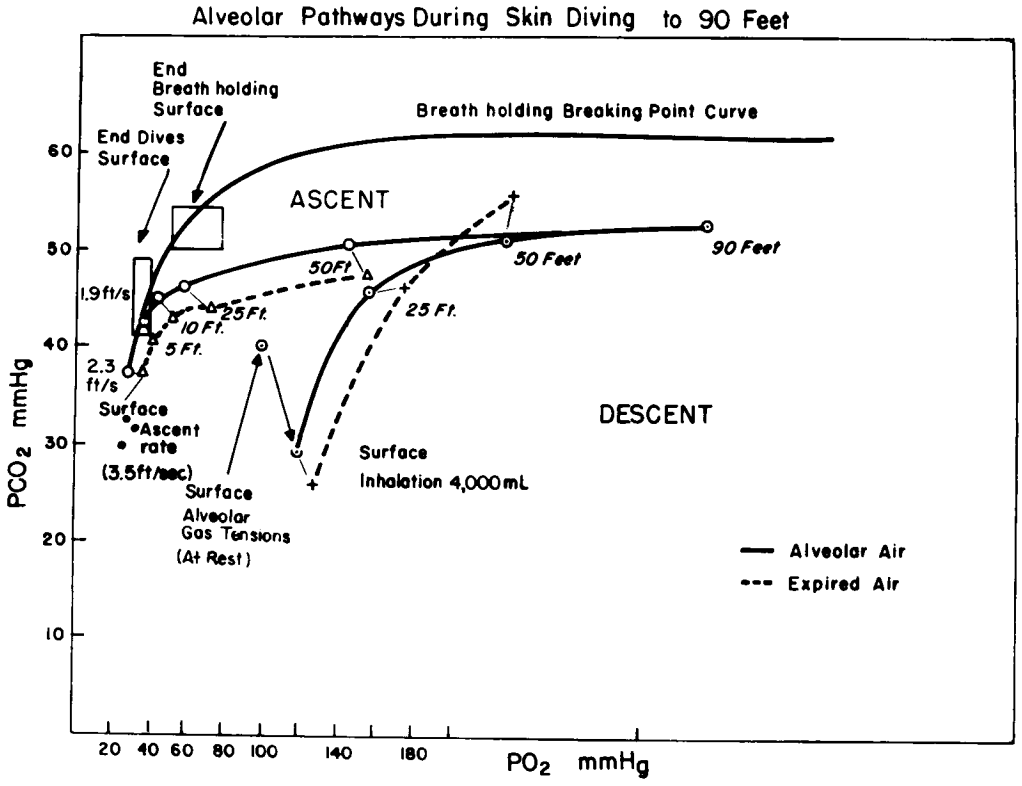

Figure 1. Alveolar Pathways during Breath-holding Dives to 90 Feet Showing Reversed CO_2 Gradient. At 50 feet P_{CO_2} mixed expired air is 6 mm Hg higher than P_{CO_2} "alveolar air." Surface breath-holding breaking point curve drawn for comparison with diving breath-holding curve. End dive alveolar P_{CO_2} decreased with increasing rate of ascent reaching 30 mm Hg at 3.5 ft/sec. (Reprinted from Science by permission.)

resting respiratory alveolar P_{CO_2} of 40 mm Hg was lowered to 29.5 mm Hg by the inhalation of four liters of air. The alveolar P_{O_2} increased correspondingly. During ascent, the increasing pressure of the water compresses the lungs and the alveolar gas tensions are quickly elevated. At 25 feet, alveolar P_{CO_2} reached 46 mm Hg. The normal "virtual" venous (oxygenated venous blood) P_{CO_2} is 48 to 50 mm Hg, which corresponds to the crossover point between CO_2 elimination and reabsorption (Figure 1). At this point CO_2 is already transferred from the lung alveoli into the pulmonary capillary blood, a condition which is indicated by the disappearance of the normal gradient between CO_2 tensions in mixed expired and alveolar air. At 50 feet, P_{CO_2} in mixed expired air is 6 mm Hg higher than the alveolar P_{CO_2}. At 90 feet, only mixed expired samples could be obtained because of the small lung volume. However, it can be assumed that under these conditions mixed expired air and alveolar gas tensions have reached an equilibrium. In spite of the large ambient water pressure increase, there is little change in the measured alveolar P_{CO_2} between 50 and 90 feet of depth because of the CO_2 uptake in the blood. During ascent alveolar P_{CO_2} falls less than would

be predicted from the ambient pressure decrease because CO_2 is again entering the lungs from the blood. The influx of CO_2 into the lungs during ascent is regulated by the speed of ascent.

The three different rates of ascent listed in Figure1, 1.9 ft/sec, 2.3 ft/sec and 3.5 ft/sec result in successively lower alveolar Pco_2 levels being attained on reaching the surface.

A quantitative estimation of the CO_2 transfer is given in the changes in the CO_2 content of the lungs (Figure 2). The CO_2 content decreased linearly from 163 ml to 89 ml during descent to 90 feet. Seventy-four ml of CO_2 were transferred into the blood during descent to 90 feet which lasted 50 seconds on the average. During the first part of ascent to 50 feet the CO_2 content of the lungs remained at the level attained at 90 feet. Only in the latter part of the ascent was the normal CO_2 gradient re-established as the lungs started to refill with CO_2.

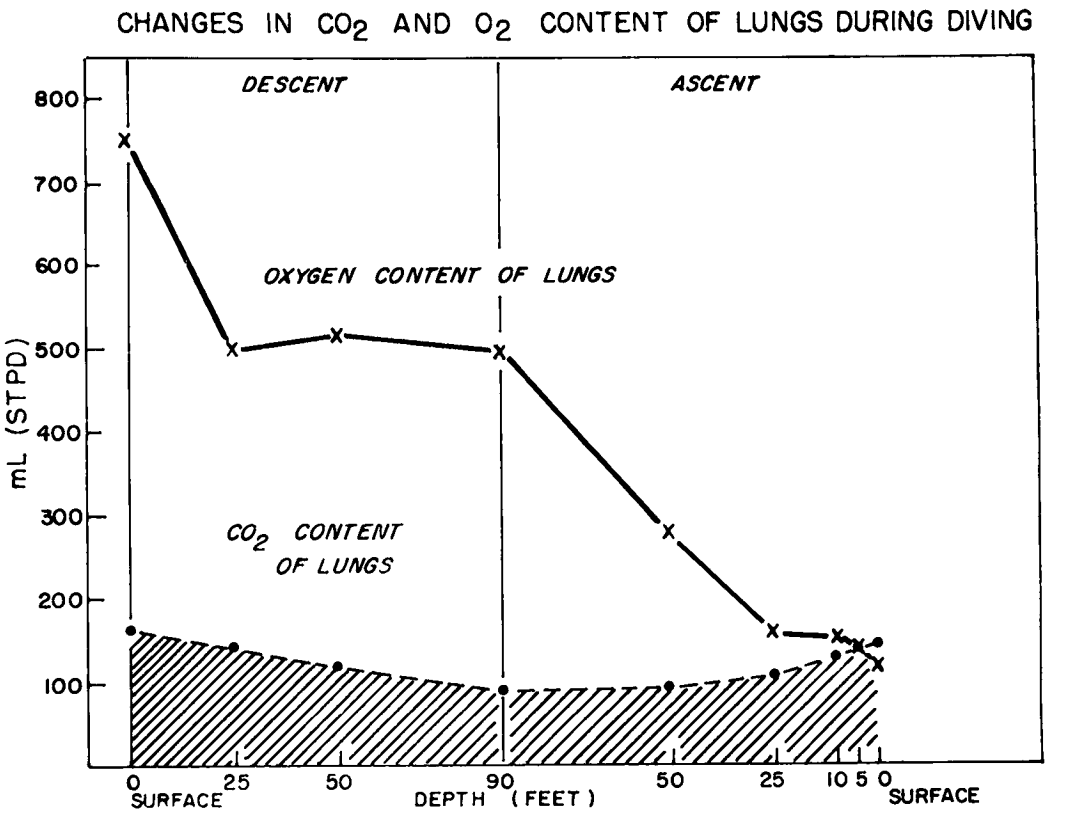

Figure 2. CO_2 and O_2 Content of Lungs during Diving (milliliters, STPD) Calculated from Measured Gas Tensions and Volumes of Mixed Expired and Alveolar Air at Various Depths, the known Residual Volume and the Total Dry Gas Pressure in the Lungs. (Reprinted from Science by permission.)

The O_2 content of the lungs does not change linearly. During the 15 seconds of effortless descent to 25 feet, 250 ml of O_2 are transferred from the lungs while the estimated O_2 consumption (based on O_2 uptake during resting) is 59 ml during this period. No further O_2 transfer occurs during descent from 25 to 90 feet. Climbing up the line during ascent results in another decrease in O_2 content which does not cover the O_2 cost during this period. Toward the end of the dive, the O_2 transfer is reduced to minimal values.

The extremely low O_2 tension found after surfacing, following a one and one-half minute dive to 90 feet, indicates the existing danger of hypoxia. One of our subjects became briefly unconscious upon reaching the surface but recovered after the first deep breath. His alveolar O_2 concentration was 3.5 per cent (Po_2 = 28 mm Hg). With a very low O_2 content and a normal or below normal CO_2 content, the nitrogen content of the alveolar air at the end of the dive is of course markedly increased, 89 per cent compared with a normal 79 per cent.

The three factors: 1) transfer of CO_2 from the lungs during dives, 2) oxygen utilization and 3) nitrogen transfer into the blood associated with the mechanical compression of the thorax as the subject descends, produce a progressive shrinking of the total chest volume during descent.

ADAPTATION PROCESSES TO BREATH-HOLD DIVING

Since the skin diver is exposed to rather high CO_2 tensions and low O_2 tensions during the breath-hold dive, one would expect to find an adaptation to high CO_2 and low O_2.

The ventilatory response to 10.5 per cent CO_2 was measured in a group of laboratory personnel serving as controls, and in a group of instructors at the Submarine Escape Training Tank. The response to CO_2 was found significantly reduced in the latter group. Moreover, the trained divers (instructors) showed a better oxygen utilization (low ventilation per liter oxygen uptake) and accepted a significantly larger debt during 33 minutes of exposure to 10.5 per cent O_2 than the group of laboratory personnel[8].

The CO_2 tolerance curves were obtained by exposing subjects for 15 minutes to 3.3, 5.4 and 7.5 per cent CO_2. Alveolar ventilation and alveolar gas CO_2 tensions were determined at the end of each exposure period. The stimulus response curves (or tolerance curves) to CO_2 showed, in the case of the tank instructors, a shift to the right and a decreased slope[1,9]. The high tolerance to CO_2 is developed during the diving period and lost after a three-month layoff period as shown in CO_2 sensitivity tests in eight tank instructors[10]. Blood gas and electrolyte changes observed at the end of a longer period of water work were similar to those noted during adaptation to prolonged exposure to CO_2[11]. They consisted in a decrease in pH, increase in Pco_2 and bicarbonate levels commensurate with an increase in hematocrit and a red cell cation exchange, e.g., increase in red cell sodium and decrease in red cell potassium. These adaptive changes disappeared after a three-month layoff period[10]. Furthermore, evidence of an increase in CO_2 stores, as the result of diving, was recently obtained in instructors following a two-year period of water work when compared with data obtained after a three-month layoff period[12]. During constant

hyperventilation lasting for one hour, more CO_2 was eliminated and the end-tidal CO_2 tension was significantly elevated under the first condition. The decreased sensitivity to CO_2 and low O_2 found in skin divers represents an adaptation similar to that observed in diving animals[13].

The lung volumes of divers were also found to change during prolonged training[14]. 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 decreased. The maximum average depth a diver can reach without getting a thoracic squeeze depends on the ratio of total lung capacity to residual capacity and the volume of the airways. The observed change in his ratio results in a 20 to 30 foot extension in the maximum safe depth after one year of duty. The changes in lung volumes, consisting of an increase in total lung capacity, vital capacity and tidal volume, and decrease in residual volume, might contribute to the reduced sensitivity to CO_2 because of the relationship found between large tidal volume, slow respiratory rate and low response to CO_2[15].

ADAPTATION TO SCUBA AND DEEP SEA DIVING

SCUBA Diving. Using open or closed circuit Self Contained Under Water Breathing Apparatus (SCUBA) units at a greater depth, the direct effect of pressure produces an increased density of the breathing mixture resulting in an increased breathing resistance. Under these conditions, the work of breathing was found increased in both breathing apparatus and in the airways of the diver[16,17]. Pulmonary resistance at four atmospheres pressure increased twofold compared with the values at sea level[18]. Froeb[19] compared the respiratory response to CO_2 in 16 professional divers using SCUBA equipment with those of non-divers and did not find any evidence of adaptation to CO_2 in the SCUBA divers. In studies of well trained underwater swimmers of the U.S. Navy Underwater Demolition Team (UDT) and untrained swimmers (laboratory personnel), using a closed circuit oxygen breathing apparatus, a higher mean end-tidal P_{CO_2} tension was found in the trained swimmers during dives at a speed of 1.1 to 1.8 km/hr[20,21]. For resting conditions under water, differences were insignificant. The end-tidal P_{CO_2} values of the trained swimmers ranged from 46.2 to 52.1 mm Hg as compared with 37.4 to 38.5 mm Hg in the control group. The higher end-tidal P_{CO_2} values of the UDT men were found to be associated with a better oxygen utilization as indicated in the lower oxygen equivalent of 19.1 to 20 liters ventilation per liter of O_2 uptake compared with 21.3 to 24.6 in the controls. The trained swimmers showed a characteristic breathing pattern of slow deep breaths with long post-inspiratory pauses. They also had a larger tidal volume than the control group. These findings indicate a measure of CO_2 adaptation similar to that found in skin divers reported above.

Furthermore, adaptation to increased work of the inspiratory muscles might have contributed to the elevated P_{CO_2} in the trained underwater swimmers because it was shown that the alveolar P_{CO_2} increases linearly with the workload of the inspiratory muscles[22].

Deep Sea Diving. In deep sea diving (hard hat diving), in which the conventional suit and helmet are used, a large amount of air has to be ventilated to prevent an accumulation of CO_2. Often this may not be fully accomplished. Moreover, at greater depths breathing resistance becomes very marked and might easily lead to CO_2 retention. Lanphier found that a considerable number of experienced deep sea divers at the U. S. Navy Experimental Diving Unit showed a retention of CO_2 during underwater work[23,24]. The respiratory minute volume declined during work dives to moderate depth using oxygen-nitrogen mixtures. The degree of retention of carbon dioxide was found to be inversely related to the ventilatory response to CO_2[25]. When breathing resistance was reduced by the use of helium-oxygen mixtures, the CO_2 retention was small or absent.

A more detailed account of adaptation in diving has been given elsewhere[26].

CONCLUSION

There is evidence showing that adaptation to CO_2 takes place during prolonged training in breath-hold diving, SCUBA diving and deep sea diving. Increased tolerance to CO_2 allows the diver to stay longer under water and appears to be a favorable form of adaptation which has also been successfully developed in diving animals. However, adaptation to CO_2 also has unfavorable consequences. These are related to the different adaptabilities of various functional systems to CO_2 which have been discussed in detail elsewhere[27]. During adaptation to 3 per cent CO_2 a gain in metabolic circulatory efficiency is achieved as indicated in an improved oxygen utilization in liters per minute at different workloads (oxygen equivalent). On the other hand mental activity remained impaired and chronaxia values elevated as long as the subjects were under 3 per cent CO_2[28]. Moreover, there is adequate experimental support from studies in man and animals indicating that the two phases of CO_2 induced respiratory acidosis were associated with a period of excitation and depression of the central nervous system (CNS) and autonomic system[29]. The decreased excitability of the CNS associated with the second phase of CO_2 adaptation is not reversed as long as the subjects are exposed to CO_2[30].

These findings lead to the conclusion that the CNS cannot adapt to the depressant effects of CO_2[27]. Achievement of CO_2 adaptation in diving is therefore considered a mixed blessing.

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SIXTH SESSION
OTHER DIVING STRESSES

J. Hardy, Chairman

DISCUSSION

HARDY: Captain Beckman, we had a diving accident off the coast of Connecticut just this past week end in which a young SCUBA diver was lost for no apparent reason. I had wondered if this might not have been due to confusion, perhaps due to low temperature. In World War II it was shown that if the skin temperature is lowered very gradually there is a tendency to by-pass one of the strong stimuli which evoke thermo-regulatory responses, namely the sensation of cold. When an individual wears a diving suit he doesn't feel cold, he just gradually becomes hypothermic. Would you comment about this possibility in terms of your plans to provide external heat to the diver?

BECKMAN: We have not done temperature measurements on men wearing the foam rubber suits, but certainly I think your comment describes the experience of people who wear them. They don't respond as drastically to maintain body temperature as the individuals we are using in our studies. We put our subjects into cold water immediately. Their response, if they are going to have it, is a very drastic one and an immediate one. But there is a difference even in the way different subjects react. As I mentioned, one individual has a very severe stress reaction to cold and fights to maintain his body heat, whereas the other individual, with almost the same body build, has almost no catecholamine excretion. He just sits in the water and gets cold.

HARDY: Do you think that the diver should perhaps be provided with some form of skin thermometer to show a dangerous level of skin temperature as an indication of body temperature?

BECKMAN: In our experience, the individual himself has no idea of how he is doing. Subjects are all happy up to the time when they decide it is time to get out of the water, but then they are aggressive, are mentally cloudy and are not reasonable. We never had anybody lose consciousness, but the subjects are definitely dulled mentally. I hope that some of the diving officers will be able to make measurements on exactly how temperature loss in divers does affect their performance.

HARDY: Captain Behnke had the experience of being cooled down in a water tank and then on being brought out, had a further drop in temperature.

BEHNKE: The secondary drop in body temperature is extremely interesting. I believe that in severe exposure we have lost a number of men who were removed from cold water quickly but were not rewarmed soon enough. The time it takes to return to normal temperature will be related to the amount of tissue that has been cooled. The temperature we were exposed to was about 48° F for a

period of one hour, which evoked a 3° F decrease in body temperature. So we did not get down into the state where the sensorium was affected. Channel swimmers must maintain circulation of blood through their muscles and if their deep body temperature drops even a small amount, they must come out of the water. In other words, they maintain body temperature. How they maintain it is truly a fascinating problem.

There is one other matter. During the early days of helium-oxygen diving, we learned that a body surrounded with helium loses a great deal of heat by conduction. Under these circumstances it is necessary to provide heat. How are you going to heat such a diver? At that time, the divers, during a phase of decompression, were surrounded with oxygen. The problem was to make an electrically heated suit which, in an oxygen atmosphere, would not incinerate the diver. In the late 1930's this was accomplished by making the suits of glass wool. It was found that about twice as much heat was required through the electrically heated suits to keep the body warm in a helium atmosphere when compared with an air atmosphere.

ERDE: In Hawaiian waters the temperature is about 74° F. The temperature drop in our SCUBA divers had a considerable amount of individual variation, from no change at all in an hour, to as much as four or five degrees.

MACKAY (S): Have you investigated the use of radio transmitters to give a better estimation of where heat is coming from and going to throughout the body?

BECKMAN: We do better than simple measurement of rectal temperatures. We make three temperature measurements; esophageal, tympanic membrane and rectal. Skin temperatures, as far as I am concerned, are very evanescent in water. The temperatures that are really meaningful are deep temperatures and there is one way to get them and that is to use deep probes of various types.

RAHN: Since a region like Hawaii has been brought up you might like to know about the Korean diving women. They are swimming in this month of February, in Pusan Harbor in water temperatures of 10°. They can stay in on the average of about 20 minutes, until they come back and warm themselves by the fire. Their oral temperatures, which we have been able to measure throughout the year, drop from 37° to 34° during this 20 minute period. Here is a wonderful chance to study people who really expose themselves every day to rather cold temperatures.

HARDY: Actually women have more peripheral fat than men. The thermal conductivity coefficient for a woman is only about one-half of that for a man in air and would be about the same in water as in air. Captain Beckman, has anyone determined the heat transfer coefficient of the skin for a man lying still in water? This is an important constant and ought to be measured.

BECKMAN: I have seen some such data but have never been satisfied with it.

HARDY: It is considered that the skin goes down to the temperature of the water. If this absolutely were the case, there would not be any heat transfer. This isn't so.

PERKINS: Is there not some evidence that fat may actually change its form, may crystalize to a certain extent, give off a latent heat of crystalization which may contribute to the insulating value of the fat? I wonder how far understanding of this has been advanced?

HARDY: The fat does change its characteristics but I believe it is not either an endothermic or exothermic reaction.

HARDY: Dr. Peterson, do you think there would be any possibility of developing analogs that would be sufficiently manageable to simulate this problem of cardiovascular response to pressure, including, let us say, the dynamics of the cardiovascular system itself, the neurophysiological and endocrine responses?

PETERSON: One can certainly develop analogs, but whether they are reliable or not always remains to be seen. There are not many responses of the cardiovascular system that are well explained. We really don't know why exercise produces the kind of changes that it does, or why temperature, heat stress, cold stress or eating produce changes. We do not have a very good set of analogs for circulation, therefore, it would be awkward to count on great immediate gains from application of analogs to diving. I was really intrigued after looking at some of the potential effects of diving. Until the necessary research is actually done and the measurements made, I don't know how anyone could predict what effects will occur.

LANPHIER: It is important to recognize the transmission of hydrostatic pressure throughout the body in diving. This should minimize pressure differentials and forcing of fluids from one part of the body to another.

LAMBERTSEN: I propose that, as in other situations, man is a good analog of himself and that studies on man will provide the most direct information soonest. There has been very little effort to study circulatory physiology under water in the past and it is about time that circulation is given attention instead of concentrating entirely upon the physiology of respiration under water. Some gains will come from experiments using immersion to approximate some effects of the weightless state.

When one stands erect in the water, an entirely different hydrostatic situation exists than we have here in air where the pressure is the same over the entire external surface of the body. When erect, the external pressure is high on the lower extremities, but lower than at mean heart level in the face and neck. When we turn upside down the situation is the opposite. The actions of this external hydrostatic column, about equal in pressure to that of the columns of blood in the vessels, should have considerable influence upon blood distribution.

RAHN: Are you now diving or are you standing in water?

LAMBERTSEN: I was commenting about the transition from standing in water to assuming the inverted position.

HARDY: Dr. Peterson mentioned an important vascular adjustment in animals, namely the closing down of peripheral circulation, particularly to the

muscles and to the fatty tissues, thus their conversion into a "smaller animal." There has been a series of studies on the seal, the alligator and the duck.

REHMAN: Animals plunged into water in such experiments, may merely be subjected to changes in tactile stimuli. Measurements have been made of the skin temperature of a free swimming porpoise using a differential type of thermistor method, with one thermistor in the water and the other attached to the animal. Information was transmitted at 250 kc to a receiver on shore. The complicating question arose concerning the relation of skin temperature to the animal's body temperature. The arrangement of the vasculature in the porpoise is quite different from that in most every other animal, even though we are dealing with a warm blooded mammal. There is a highly developed arteriolar bed immediately beneath the skin. The skin is only about 1 mm thick and the arteriolar bed is above the fat layer. The question has been raised as to whether the fat still may serve as an insulating medium when the fat layers are in the "wrong place." The fat is deeper than the arteriolar bed and yet in temperature measurements made on these animals, it was found that where areas of greater turbulence developed, the differential temperature between the skin and the water was higher. The skin temperature was not equivalent to that of the water so that there seem to be differences in circulation. May we then not be dealing with the same thing in the human? I think Dr. Beckman mentioned that the temperature in the toes and the fingers were lower than in other parts of the body. If the circulation to the hands could be increased by some means, could not that protect function in spite of the heat loss, rather than adding three inches of insulation?

HARDY: Dr. Schaefer, are there any measurements on how the divers respond to altitude after they have been chronically adapted to the stresses of increased pressure?

SCHAEFER: We only have studied the respiratory response to low oxygen, corresponding to the response at altitude. It was reduced.

HARDY: Do they have a higher exercise tolerance?

SCHAEFER: This we have not done.

BEAN: Do you suppose that the decreased respiration of trained divers is a result of the decreased diameter of the small respiratory passages? Dr. DuBois mentioned in a previous session that respiration at high ambient pressure could lead to decreased bronchiolar diameter. The little passageways would constrict simply due to the high velocity of the air passing through them.

HARDY: I have wondered if anyone has calculated the velocities through these small bronchioles and estimated the Bernoulli effect.

CRAIG: Dr. Schaefer commented that he did not see any "diving bradycardia" in man which was different from the known bradycardia of breath-holding. We have been trying to study the diving bradycardia in man. Scholander and others have described a "diving reflex." On the basis of our studies I would suggest that these cardiovascular responses should be considered as strains resulting from multiple stresses. What has been called a "diving reflex" is more likely the result of "diving reflexes."

In man there are many strains he is exposed to when diving. First of all, he takes a large inspiration and single large inspiration and expiration. On entering water the surface temperature will drop as a result of exposure to water and due to peripheral vasoconstriction. All of these experimental dives involved in pulse rate studies are apneic dives, which implies breath holding. As you take a maximual inspiration and then relax, there is a relaxation pressure with a change in intrapleural pressure of a Valsalva type. As for the problem of the subject being in water and not air, some information indicates that the venous pressure-volume relationships are on a different part of the compliance curve. In terms of the arterial pressures, I can think that perhaps that when you take a large inspiration you have a Valsalva type of pressure. We have some evidence to indicate that the course of the heart rate changes. For all of these reasons it is not justifiable to talk about any bradycardia of diving as a diving reflex. It deserves attention first in the light of known physiological mechanisms.

SYMPOSIUM ATTENDEES

LCDR B. F. Ackerman, RCN
RCN Diving Est. West
HMC Dockyard
Esquimalt, British Columbia

Mr. Ord Alexander
Underwater Storage, Inc.
1028 Connecticut Avenue, N.W.
Washington, D.C.

LT Howard Alfondre, MC USN
U.S. Naval Submarine School
New London, Connecticut

CAPT Harry F. Alvis, MC USN
U.S. Naval Shipyard
Quarters P, Naval Base
Charleston, South Carolina

Mr. C.D. Anderson
TRACOR
4928-A St. Elmo Avenue
Bethesda, Maryland

LCDR C. F. Aquadro, MC USN
Bureau of Medicine and Surgery
Code 752
Washington 25, D.C.

LCDR R.T. Arnest, MC USN
Staff, Naval Hospital
Philadelphia, Pennsylvania

Safuh Attar, MD
University Hospital
University of Maryland
Baltimore 1, Maryland

CDR Theodore F. Bacheler, USN
Code 638 Bureau of Ships
Washington 25, D.C.

LCDR Frank Barrett, USN
Experimental Diving Unit
U.S. Naval Station
Navy Yard Annex
Washington 25, D.C.

LCDR A. Barsoum, MC USN
Deep Sea Diving School
U.S. Naval Station
Navy Yard Annex
Washington 25, D.C.

Dr. L. Barthelemy
Groupe d'Etudes et
de Recherches Sous-Marines
Toulon, France

Dr. R.G. Bartlett
Applied Physics Laboratory
Johns Hopkins University
8621 Georgia Avenue
Silver Spring, Maryland

Mr. George Bass
University of Pennsylvania Museum
University of Pennsylvania
Philadelphia, Pennsylvania

Mr. John Beagles
Code 4121
U.S. Navy Electronics Laboratory
San Diego 52, California

John W. Bean, MD
Department of Physiology
University of Michigan Medical School
Ann Arbor, Michigan

Norwin H. Becker, MD
Histopathology Section
Montefiore Hospital
New York City, New York

CAPT E.L. Beckman, MC USN
U.S. Naval Medical Research Institute
National Naval Medical Center
Bethesda, Maryland

CAPT A.R. Behnke, MC USN (Ret)
3350 Divisadero Street
San Francisco, California

Mr. Morton Belkin
U.S. Naval Material Laboratory
Brooklyn, New York

Dr. Peter B. Bennett
Royal Naval Physiological Laboratory
Alverstoke, Hants, England

LT de VAISSEAU F. Besse
Porte-Helicoptere "Le Resolue"
Brest, France

Dr. Helmut Bohnenkamp
Marschweg 132
Oldenburg
Federal Republic of Germany

Herr Wolfral Bohnenkamp
Marschweg 132
Oldenburg
Federal Republic of Germany

CAPT George F. Bond, MC USN
Officer-in-Charge
Naval Medical Research Laboratory
Submarine Base
New London, Connecticut

LCDR Robert C. Bornmann, MC USN
Laboratory of Pharmacology
University of Pennsylvania
Schools of Medicine
Philadelphia 4, Pennsylvania

Dr. Hugh Bradner
Institute of Geophysics
University of California
La Jolla, California

Mr. Kenneth Breisch
Code 467
Office of Naval Research
Washington 25, D.C.

Ivan Brown, Jr., MD
Department of Physiology
School of Medicine
Duke University
Durham, North Carolina

Dr. Albert A. Buhlmann
Cardio-Pulmonary Laboratory
Kantonspittal
University of Zurich
Zurich, Switzerland

LTJG Stephen Bullock, USN
Code 638.2 Bureau of Ships
Washington, D.C.

Frank W. Bussard, MD
202 Whitcomb and Keller Building
South Bend, Indiana

Dr. Leonard Caranna
Life Systems Division
McDonnell Aircraft Corporation
St. Louis, Missouri

Mr. C.R. Carey
Physiology Branch
Naval Medical Research Laboratory
Submarine Base
New London, Connecticut

Dr. Frank Carpenter
Department of Physiology
Dartmouth Medical School
Hanover, New Hampshire

Dr. David Chapman
Project Leader
Bioastronautics Section
Aero Space Division
Boeing Aircraft Corporation
Seattle, Washington

Mr. James Clark
Laboratory of Pharmacology
University of Pennsylvania
Schools of Medicine
Philadelphia 4, Pennsylvania

CAPT D.N. Clay, USN
Op 343 E
The Pentagon
Washington 25, D.C.

Mr. T.J. Cosgrune
Naval Research Laboratory
Washington 25, D.C.

Mr. Frank Cowan
American Machine and Foundry Corp.
P.O. Box 187, Station F
Buffalo 12, New York

R.A. Cowley, MD
Department of Surgery
University of Maryland Hospital
Baltimore 1, Maryland

Albert B. Craig, Jr., MD
University of Rochester
School of Medicine and Dentistry
Rochester 20, New York

LT COL J.D. Craig, USA (Ret)
John D. Craig Productions
50 Ontare Road
Arcadia, California

Mr. A.R. Dasler
Naval Medical Research Institute
National Naval Medical Center
Bethesda, Maryland

LT Donald R. Davis, USN
Fleet Submarine Training Facility
U.S. Naval Submarine Base
Navy No. 128, FPO
San Francisco, California

Dr. Albert Dawe
Office of Naval Research
Branch Office
86 East Randolph
Chicago 1, Illinois

James G. Dickson, MD
Laboratory of Pharmacology
University of Pennsylvania
Schools of Medicine
Philadelphia 4, Pennsylvania

C. Digiovanni, MD
Human Factors Branch
Aviation Medical Acceleration Laboratory
U.S. Naval Air Development Center
Johnsville, Pennsylvania

COL Theodore Domanski, USAF
Chief, Toxology Department
USAF Medical Service Corps
Armed Forces Institute of Pathology
Washington 25, D.C.

Dr. J.H. Dougherty, Jr.
Physiology Branch
Naval Medical Research Laboratory
Submarine Base
New London, Connecticut

John J. Downes, MD
Laboratory of Pharmacology
University of Pennsylvania
Schools of Medicine
Philadelphia 4, Pennsylvania

Arthur B. DuBois, MD
Laboratory of Physiology and
Pharmacology
University of Pennsylvania
Graduate School of Medicine
Philadelphia 4, Pennsylvania

CAPT Gerald J. Duffner, MC USN
Submarine Medicine Division
Bureau of Medicine and Surgery
Washington 25, D.C.

LCDR T.S. Dunn, Jr., MC USN
Normal and Pathological Physiology
Department
National Aeronautics and Space Adm.
Washington 25, D.C.

LT John Dwyer, USN
U.S. Naval Submarine School
New London, Connecticut

Mr. Peter Edel
Schlumberger Well Surveying Corp.
P.O. Box 307
Ridgefield, Connecticut

SURG CAPT F.P. Ellis, RN
Office of the Commander
British Navy Staff
P.O. Box 165
Benjamin Franklin Station
Washington, D.C.

Mr. J.H. Emerson
J.H. Emerson Company
22 Cottage Park Avenue
Cambridge 40, Massachusetts

LT Allen Erde, MC USN
U.S. Naval Submarine Base
Navy No. 128, FPO
San Francisco, California

W.G. Esmond, MD
Department of Surgery
University of Maryland
School of Medicine
Baltimore 1, Maryland

Mr. E. Ethell
ACR Electronics
551 West 22nd Street
New York City, New York

Mr. F. Fegan
Mt. Sinai Hospital
New York 29, New York

CDR J.E. Fleming, USCG
U.S. Coast Guard Building
1300 E Street, N.W.
Washington 25, D.C.

LT R.T. Fleming, USN
Commanding Office
U.S. Naval School Underwater Swimmers
U.S. Naval Base
Key West, Florida

Mr. Michael J. Foran
Code 638 Bureau of Ships
Washington 25, D.C.

Robert Forster, MD
Laboratory of Physiology and Pharmacol.
University of Pennsylvania
Graduate School of Medicine
Philadelphia 4, Pennsylvania

Dr. Warner Fricke
Bell Aerosystems Company
P.O. Box 1
Buffalo 5, New York

CAPT Robert H. Fuller, MC USN
Armed Forces Institute of Pathology
Washington 25, D.C.

Mr. Robert Gelfand
Laboratory of Pharmacology
University of Pennsylvania
Schools of Medicine
Philadalphia 4, Pennsylvania

Dr. D.L. Gilbert
National Institutes of Health
Bethesda, Maryland

H. William Gillen, MD
Edward J. Meyer Memorial Hospital
Buffalo 15, New York

CDR W.E.B. Godsal, RN
British Navy Staff
P.O. Box 165
Benjamin Franklin Station
Washington, D.C.

Mr. Loyal Goff
Program Director
Office of Institutional Programs
National Science Foundation
Washington 25, D.C.

LT M.W. Goodman, MC USN
Experimental Diving Unit
U.S. Naval Station
Navy Yard Annex
Washington 25, D.C.

Dr. Sheldon F. Gottlieb
Linde Air Products Company
30 East 42nd Street
New York 17, New York

Dr. Charles Gowdey
University of Western Ontario
Faculty of Medicine
London, Canada

Dr. Leon J. Greenbaum, Jr.
Department of Physiology
School of Medicine
University of Maryland
Baltimore, Maryland

Mr. W.H. Hamilton, Jr.
104 St. Bernard Drive
Vienna, Virginia

CDR E.C. Hannen, RN
Commanding Officer
Admiralty Experimental Diving Unit
c/o HMS VERNON
Portsmouth, Hants, England

James D. Hardy, MD
Professor and Director of Physiology
John B. Pierce Found. of Conn., Inc.
290 Congress Avenue
New Haven, Connecticut

Mr. William F. Hardy
San Diego Divers Supply
Midway Drive
San Diego, California

Dr. Niels Haugaard
Laboratory of Pharmacology
University of Pennsylvania
Schools of Medicine
Philadalphia 4, Pennsylvania

William M. Helvey, MD
Applied Research and Development
Republic Aviation Corporation
Farmingdale, Long Island, New York

Mr. H.V. Hempleman
Royal Naval Physiological Laboratory
Alverstoke, Hants, England

Dr. Edward Hendler
Life Sciences Research Group
Air Crew Equipment Laboratory
Naval Air Engineering Center
Philadelphia 12, Pennsylvania

Dr. Carl M. Hesser
Laboratory of Aviation and Naval Medicine
Karolinska Institute
Stockholm, Sweden

A. Heyman, MD
Department of Pharmacology and Physiology
Duke University Medical Center
Durham, North Carolina

CAPT Yoshitsuga Hiruma
MC Japanese MSDF
U.S. Naval Submarine School
New London, Connecticut

LT M.M. Hoffer, MC USN
U.S. Naval School
Underwater Swimmers
U.S. Naval Base
Key West, Florida

Dr. George N. Hoover
Physiology Life Sciences
North American Aviation
Downey, California

Mr. John R. Houchen, Jr.
Code 4121
U.S. Navy Electronics Laboratory
San Diego 52, California

Dr. Wayland E. Hull
Department of Physiology and Pharmacology
Duke University
Durham, North Carolina

Mr. Lee M. Hunt
Mine Advisory Committee
National Academy of Sciences
National Research Council
Washington 25, D.C.

J.H. Jacobson, MD
Mt. Sinai Hospital
New York 29, New York

Dr. Lloyd A. Jeffress
Defense Research Laboratory
P.O. Box 8029
Austin, Texas

Mr. Robert Jones
Westinghouse, Incorporated
Baltimore, Maryland

Mr. J. H. Jory
American Submarine Company
101st and Calumet Streets
Chicago, Illinois

SURG LCDR E. R. Keirstead, RCN
Staff Officer Medical Services
Canadian Joint Staff
2450 Massachusetts Avenue, N.W.
Washington 8, D.C.

Mr. Hannes Keller
Bleichestrasse 15b
Winterthur, Switzerland

ENS P. E. Kelly, USN
Explosive Ordnance Disposal Facility
Naval Propellant Plant
Indian Head, Maryland

LT Harry Kennedy, MC USN
U.S. Naval Submarine School
New London, Connecticut

CAPT J. L. Kinsey, MC USN
Special Projects Office
Munitions Building
Washington 25, D.C.

Mr. Allan R. Krasberg
808 Raleigh Road
Glenville, Illinois

LT Marvin Kripps, MC USN
U.S. Naval Submarine School
New London, Connecticut

Miss Suzanne Kronheim
Code 441
Office of Naval Research
Washington 25, D.C.

Christian J. Lambertsen
Laboratory of Pharmacology
University of Pennsylvania
Schools of Medicine
Philadelphia 4, Pennsylvania

LCDR R. E. Lanphear, USN
Code 467
Office of Naval Research
Washington 25, D.C.

E. H. Lanphier, MD
Department of Physiology
University of Buffalo Medical School
Buffalo, New York

Dr. David Leith
Harvard University School of
Public Health
Boston 15, Massachusetts

Dr. Leonard M. Libber
Code 441
Office of Naval Research
Washington 25, D.C.

Mr. J. D. Libbey
Ethyl Corporation
1728 N Street, N.W.
Washington 6, D.C.

Mr. Edwin A. Link
Link Engineering Corporation
Binghamton, New York

Dr. D. M. Long
Naval Medical Research Institute
National Naval Medical Center
Bethesda 14, Maryland

Dr. E. Croft Long
Department of Physiology and
Pharmacology
Duke University Medical Center
Durham, North Carolina

George P. Lord, MC USN
Physiology Branch
Naval Medical Research Laboratory
Submarine Base
New London, Connecticut

SURG LCDR D. E. Mackay, RN
Staff, Royal Navy Physiology Lab.
Alverstoke, Hants, England

Dr. R. Stuart Mackay
School of Optometry
University of California
Berkeley, California

CAPT D. Maio, MC USAF
Department of Physiology
University of Buffalo
Buffalo, New York

Mr. K.L. Malick
Scott Aviation Corporation
225 Erie Street
Lancaster, Pennsylvania

Dr. Chester M. McKinney
Defense Research Laboratory
P.O. Box 8029
Austin, Texas

CAPT J.H. Maurer, USN
Op 31, The Pentagon
Washington 25, D.C.

LT COL Janice A. Mendelson, MC USA
Biophysics Division
Directorate of Medical Research
U.S. Army Chemical Research and
Development Laboratory
Edgewood Arsenal, Maryland

Dr. Stanley L. Miller
School of Science Engineering
University of California
La Jolla, California

J. Morsch, MD
Grasslands Hospital
Valhalla, New York

CDR M.O. Muncie, USN
Code 466 Office of Naval Research
Washington 25, D.C.

LT Frank Nicholas, MC USN
U.S. Naval Submarine School
New London, Connecticut

CDR N.E. Nickerson, USN
Officer-in-Charge
Experimental Diving Unit
U.S. Naval Station
Navy Yard Annex
Washington 25, D.C.

Mr. W.T. Odum
U.S. Navy Mine Defense Laboratory
Panama City, Florida

Mr. W.J. O'Neill
J.H. Emerson Company
22 College Park Avenue
Cambridge, Massachusetts

CDR W.W. Palmer, RCN
D.N.F.E.R.
Naval Headquarters
Ottawa, Canada

Mr. Frank P. Payne
Admiralty Experimental Diving Unit
c/o HMS VERNON
Portsmouth, England

Jon H. Pegg, MD
The Queen's Hospital
P.O. Box 861
Honolulu 8, Hawaii

John Forbes Perkins, Jr., MD
Department of Physiology
University of Chicago
Chicago 37, Illinois

Lysle H. Peterson, MD
Department of Physiology
University of Pennsylvania
Philadelphia 4, Pennsylvania

LCDR T.D. Pfundstein, USN
Code 463
Office of Naval Research
Washington 25, D.C.

CAPT Ralph O. Phillips
Senior Staff Scientist
The George Washington University
Washington 6, D.C.

CAPT Joseph P. Pollard, MC USN
Code 107
Office of Naval Research
Washington 25, D.C.

Dr. John F. Pritzlaff
General Electric Company
Schenectady, New York

LT John Pulskamp, MC USN
U.S. Naval Submarine School
New London, Connecticut

Dr. Herman Rahn
Department of Physiology
Medical School
University of Buffalo
Buffalo, New York

Dr. Irving Rehman
Anatomy Department
University of Southern California
Medical School
Los Angeles, California

Martin Reivich, MD
Laboratory of Pharmacology
University of Pennsylvania
Schools of Medicine
Philadelphia 4, Pennsylvania

LTJG Joseph Reynolds, MSC USN
Experimental Diving Unit
Navy Yard Annex
Washington 25, D.C.

Dr. L. Rendel-Baker
Mt. Sinai Hospital
New York 29, New York

LT Julio Rivera, MC USN
Staff, Submarine Squadron Twelve
Key West, Florida

Mr. A. Roberts
General Precision, Incorporated
Tarrytown, New York

Dr. Robert M. Rosenbaum
Albert Einstein College of Medicine
Yeshiva University
Department of Pathology
New York 61, New York

Mr. David Rush
President, ACR Electronics
551 West 22nd Street
New York 11, New York

Mr. Frank Scalli
31 North Milton Street
Malden, Massachusetts

Dr. Karl E. Schaefer
Physiology Branch
Naval Medical Research Laboratory
Submarine Base
New London, Connecticut

LT David Schaible, USN
U.S. Naval School
Underwater Swimmers
Key West, Florida

LT Richard Schillaci, MC USN
U.S. Naval Submarine School
New London, Connecticut

C.F. Schmidt, MD
Laboratory of Pharmacology
University of Pennsylvania
Schools of Medicine
Philadelphia 4, Pennsylvania

Dr. Heinz R. Schreiner
Linde Air Products Company
30 East 42nd Street
New York 17, New York

CAPT John R. Seal, MC USN
Naval Medical Research Institute
National Naval Medical Center
Bethesda 14, Maryland

CDR W.F. Searle, Jr., USN
Service Force Pacific
Navy 128, Box 22, FPO
San Francisco, California

Samuel F. Seeley, MD
National Academy of Sciences
National Research Council
Washington 25, D.C.

LCDR Klaus Seeman, MC FGN
Marineoberstabsartz
243 Neustadt in Holstein
Wieksbergstr 54, Germany

Dr. Julius Sendroy
Naval Medical Research Institute
National Naval Medical Center
Bethesda, Maryland

Jack Shapiro, MD
Senior Industrial Hygiene Physician
State of New York Department of Labor
Division of Industrial Hygiene
80 Centre Street
New York 13, New York

Mr. Stanley Shatunoff
Janus Products, Incorporated
210 Michael Drive
Syosset, New York

CAPT K.G. Simmons, USN
Op 32, The Pentagon
Washington 25, D.C.

LT Thomas K. Smith, MC USN
U.S. Naval Submarine School
New London, Connecticut

Mr. Raymond E. Snyder, Manager
Roy C. Ingersol Research Center
Borg Warner Corporation
Des Plaines, Illinois

Russell D. Squires, MD
Aviation Medical Acceleration
Laboratory
U.S. Naval Air Development Center
Johnsville, Pennsylvania

LCDR C. Stahl, MC USN
Armed Forces Institute of Pathology
Washington 25, D.C.

CDR James E. Stark, MC USN
Assistant Officer-in-Charge
Naval Medical Research Laboratory
New London, Connecticut

Dr. R.O. Steiner
Swiss Embassy
Washington, D.C.

Ronald Stephen, MD
Duke University Medical Center
Durham, North Carolina

Mr. James Stewart
Chief Diving Officer
University of California
La Jolla, California

LT F. Stucker, MC USN
U.S. Naval Submarine School
New London, Connecticut

LT P. Swartz, MC USN
U.S. Naval Submarine School
New London, Connecticut

LT F. Taylor, MC USN
U.S. Naval Submarine School
New London, Connecticut

Dr. N.B.G. Taylor
Defense Research Medical Laboratory
Toronto, Canada

Dr. Robert E. Taylor
Laboratory of Biophysics
National Institutes of Health
Bethesda, Maryland

LT Joseph J. Thomas, MC USN
Staff, Naval Medical Research Institute
National Naval Medical Center
Bethesda 14, Maryland

LCDR A.T. Thorp, MC USN
U.S. Naval Submarine School
New London, Connecticut

LT Roberto Truglio, IN
Minstero Difesa
Comsubin, La Spezia, Italy

Mr. Paul Tzimoulis
Sportsways, Incorporated
7701 East Compton Blvd.
Paramount, California

O.E. Van Der Aue, MD
Medical Advisory Committee
National Academy of Sciences
National Research Council
Washington 25, D.C.

Dean Benjamin D. Van Evera
The George Washington University
Washington 6, D.C.

LT John A. Vaughn, MC USN
U.S. Naval Submarine School
New London, Connecticut

CDR Armin Wandel, MC FGN
U.S. Naval Submarine School
New London, Connecticut

Dr. W.H. Wanger
72 Three Acre Road
Groton, Connecticut

Carl E. Wasmuth, MD
Department of Anesthesiology
Cleveland Clinic
Cleveland, Ohio

LCDR W.E. Webber, USN
ComPhibPac
Fleet Post Office
San Francisco, California

James L. Whittenberger, MD
Harvard University
School of Medicine
Cambridge, Massachusetts

Group CAPT J.C. Wickett, RCAF
Office of the Surgeon General
National Defense Headquarters
Ottawa, Canada

Kirkley R. Williams, MD
Laboratory of Pharmacology
University of Pennsylvania
Schools of Medicine
Philadelphia 4, Pennsylvania

LT JG Dale Wise, MSC USN
Experimental Diving Unit
U.S. Naval Station
Navy Yard Annex
Washington 25, D.C.

Dr. August F. Wittenborn
TRACOR
Austin, Texas

Dr. M. Wittner
Department of Pathology
Albert Einstein College of Medicine
New York 61, New York

Dr. Myron Wolbarscht
Naval Medical Research Institute
National Naval Medical Center
Bethesda 14, Maryland

Dr. James D. Wood
Defense Research Medical Laboratory
Toronto, Ontario, Canada

W.B. Wood, MD
Department of Medicine
University of North Carolina
Chapel Hill, North Carolina

CDR Robert D. Workman, MC USN
Experimental Diving Unit
U.S. Naval Station
Navy Yard Annex
Washington 25, D.C.

Mr. William Wright
Albert and J.M. Anderson Manufacturing Company
Boston, Massachusetts

INDEX