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CIRCULATORY ADAPTATION TO THE REQUIREMENTS OF LIFE UNDER MORE THAN ONE ATMOSPHERE OF PRESSURE

by

Karl E. Schaefer, M.D.

Bureau of Medicine and Surgery, Navy Department
Research Work-Unit MR005.14-3100-1.06

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C. L. Waite, CAPT MC USN
COMMANDING OFFICER
U.S. Naval Submarine Medical Center

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SUMMARY PAGE

THE PROBLEM

To prepare an up-to-date authoritative review article to cover the rapidly expanding field of diving and pressure physiology.

FINDINGS

In response to a request from Dr. W. F. Hamilton, Editor of the Handbook of Physiology's Section on Circulation, a paper was prepared, which appeared as Chapter 51, title - "Circulatory Adaptation to the Requirements of Life Under More Than One Atmosphere of Pressure." The chapter includes: Cardiovascular and respiratory functions and adaptations in skin diving; Hazards of skin diving and related adaptive changes; Carbon dixoide intoxication and adaptation in diving; Anoxia; Oxygen toxicity; Nitrogen narcosis; Air embolism, and Decompression sickness.

APPLICATIONS

This article provides background information for researchers in diving and high pressure physiology. It is also used for teaching submarine medical officers under instruction in the School of Submarine Medicine at the Submarine Medical Center.

ADMINISTRATIVE INFORMATION

This investigation was completed as a part of BuMed Research Work Unit MR005.14-3100-1.07 - Physiological Alterations Occurring in Free Diving. The present report is No. 6 on this Work Unit. It was approved for publication in July of 1962; submitted to Am. Physiological Soc. and subsequently published as a chapter in Handbook of Physiology -- Circulation III. A reprint of this chapter (51) received in December 1965 has been designated as Submarine Medical Research Laboratory Report No. 463.

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CHAPTER 51

Circulatory adaptation to the requirements of life under more than one atmosphere of pressure

KARL E. SCHAEFER

Physiology Branch, U. S. Naval Medical Research Laboratory, U. S. Naval Submarine Base New London, Groton, Connecticut

CHAPTER CONTENTS

LIFE UNDER MORE THAN 1 ATM PRESSURE is confined to the dense and wet environment of diving and to caisson operations. It always has been a challenge for man to explore the depths of the ocean, and the secrets of the deep fascinate his fancy.

Good accounts of the history of diving have been given by Davis (75), Larson (159) and Stelzner (239). Classic Greek and Roman literature contain references to diving and breathing-tube appliances.

Leonardo da Vinci (74) (ca. 1500) made sketches of a variety of diving appliances ranging from breathing tubes to full diving dress. However, he did not reveal designs of submarines "by means of which many people may stay some time under water" because of the "evil nature of man who would use it as means of destruction to sink ships with the men in them." In 1819, Augustus Siebe developed a diving suit and helmet which made diving operations practical. With subsequent improvement Siebe's type of diving suit is still in use today as standard equipment.

The classic studies of Paul Bert (43) on the effect of high and low pressures laid the foundation of our knowledge in this field. Haldane's (110) work led to the development of the stage decompression system which gave the diver satisfactory protection against decompression sickness. A classic description of the latter has been given by Heller *et al.* (116). Further pioneer work in the field of diving physiology was carried out by Irving (132) and Scholander (223) who contributed greatly to the understanding of adapta-

tion in diving animals. August Krogh (144) wrote a remarkable monograph, *The Comparative Physiology of Respiratory Mechanisms*, in which details of breathing apparatuses of diving animals are discussed.

There are some interesting "living prototypes" of diving appliances. For example, the whip-tailed larva (*Eristalis*) has a breathing tube consisting of a retractible outer sheath and air pipes within which do not stretch but maintain their cylindrical form; however, these air pipes can be coiled inside the body of the animal. The water spider has a perfect diving bell in which to breathe and keep dry under water which appears to be a true respiratory apparatus. The excess of carbon dioxide is dissolved in the water which gives up oxygen; this gas exchange allows the spider to remain in the diving bell for weeks at a time.

The literature on high-pressure effects comprises a vast number of clinical and experimental studies. About 7,000 references are listed in the two volumes of the *Bibliographical Source Book of Compressed Air, Diving and Submarine Medicine*, edited by Hoff and Greenbaum (125, 126).

Very few studies deal with problems of adaptation. The task of writing about circulatory adaptation to life under more than one atm is further complicated by the fact that high pressure per se has no demonstrable direct physiological effects, at least in the ranges to which man is exposed. Therefore, it is possible only to discuss the individual factors of the high-pressure environment which are known to have distinct physiological effects, and to present evidence, if any, of adaptive reactions. The reader is also referred to recent papers by Pappenheimer (190), Gauer (97), and Gregg (109) that review effects of various acute and chronic environmental changes on capillary exchange and on homeostasis of extra-arterial and arterial circulation. Some of the factors discussed, such as increased CO_2 and low O_2 play a role under conditions of life at increased pressure.

PHYSIOLOGICAL CHANGES UNDER CONDITIONS OF SWIMMING AND DIVING

If the body is submerged with the head above water, small negative pressures of about 20 cm H_2O develop in the lungs since the rest of the body is exposed to a higher pressure. In today's popular sport of spear fishing, snorkels are used and higher negative pressure occurs in the lungs depending on the depth of the water. One can still breathe through a rigid tube when submerged in 150 cm of water (167). The Viennese physiologist, R. Stigler, reached depths of 192 cm and 200 cm of water, testing the strength of the inspiratory muscles. As a result of this experiment, he contracted a heart dilatation and had to be hospitalized for 3 weeks (240). Water pressure at a depth of 150 cm corresponds to a negative pressure of 112 mm Hg in the lungs. At 200 cm of depth the extrathoracic overpressure reaches the level of the aortic pressure, 148 mm Hg.

Negative-pressure breathing at -20 to -30 cm H_2O simulates, to a certain extent, conditions of swimming and snorkeling. Cardiovascular responses during negative-pressure breathing at -30 cm of water showed in man a small fall of about 8 mm Hg in both systolic and diastolic blood pressure (78). Ting *et al.* (243) did not observe any changes in blood pressure and heart rate under these conditions. Finger plethysmographic measurements indicated peripheral venous constriction (243), which is in agreement with findings of DeLalla (77) and Fenn & Chadwick (94) who reported a decrease in peripheral blood flow during negative-pressure breathing. Furthermore, it has been established that the central venous pressure decreases under these conditions (98, 127). Gauer *et al.* (98) also showed that the circulatory changes observed during negative-pressure breathing are part of a regulation involved in maintaining the homeostasis of the extra-arterial circulation. The main feature of this volume regulatory mechanism is an increase in the filling of the intrathoracic circulation associated with a decrease in the filling of the extrathoracic circulation resulting in a water diuresis. This has been found in dogs (98) and in man (232). Immersion of the trunk in a warm bath produces similar effects (17). These findings have been interpreted as evidence for intrathoracic volume receptors which initiate increases in the rate of urine flow with expansion in thoracic blood volume (97).

Water diuresis is one of the more common observations made on instructors at the Escape Training Tank, U. S. Naval Submarine Base New London, Groton, Conn. (49). These instructors carry out repeated dives usually down to 50 feet and sometimes deeper.

Investigations of a typical diving animal, the seal, showed that it will tolerate continuous negative-pressure breathing for periods up to one hour without an increase in urine flow. This observation suggests that the seal may have some adaptive mechanism which prevents shifting of blood into the thorax (183). Possibly the inferior vena caval valve of the seal may present such an adaptive mechanism.

ANATOMICAL AND PHYSIOLOGICAL ADAPTATION OF DIVING ANIMALS

The adaptations which permit diving animals to hold their breath during prolonged submergence are of interest for an understanding of human responses during skin diving (diving without additional air supply). Land mammals in general are able to hold their breath for about 1 min whereas sponge divers can do so for up to 2 min. Muskrats can dive for about 12 min and beavers for about 15 min (124). Whales and seals are known to stay under water at great depths for a much longer time. According to Irving (132), the sperm whale has been observed to reach depths of 900 m and to remain there for 1 to 2 hours. They return directly to the surface without developing decompression sickness. This is made possible by respiratory and circulatory adaptations which were investigated by Irving (132) and Scholander (223). Scholander pointed out that diving animals, seals and whales, have small lungs with a large dead space made up by the trachea and bronchi. In these animals the dead space holds one-tenth of the lung volume while this ratio is only one-fortieth in humans. At a depth of 100 m all the air will be in the dead space and no diffusion of nitrogen or oxygen will take place. Nitrogen uptake in the tissues would be zero in this case. Nitrogen invasion into the tissues is further reduced by additional adaptive mechanisms. Pugh (198) has drawn attention to the fact that seals and whales have special air sinuses into which some of the residual air of the lungs is squeezed. Since seals also exhale before they dive, very little air is left in the lungs which under pressure become virtually solid organs.

The circulatory adjustments in diving consist primarily of an extreme slowing of the heart rate which has been observed in all diving and nondiving animals studied so far. Scholander found, during the dive of a seal, a reduction in heart rate from 120 to 10 (223). Slowing of the blood flow during diving further decreases the diffusion of nitrogen and oxygen into the tissues and so operates as to reduce metabolism during diving. Diving bradycardia develops gradually in most animals, but occurs immediately after submersion in the seal (223). It does not appear to be a simple baroceptor reflex since it can be initiated by clapping the hands (224). Irving (133) reported that the seal can extend its resources of oxygen for longer periods of time when the bradycardia develops earlier which seems to indicate that the reduction in oxygen consumption during the dive is at least initially dependent upon the rapidity with which the bradycardia develops. ECG tracings obtained in the American alligator during diving (4) showed that prolongation of both systole (50 per cent) and diastole (87 per cent) are involved in the development of diving bradycardia. In spite of the greatly reduced heart rate, systolic blood pressure was found to be maintained or increased during dives in the muskrat, duck (136), seal (134), and alligator (4). Furthermore, the systolic blood pressure rises during the slow heart beats which show an approximately normal time sequence; this is associated with a significantly prolonged diastolic fall in blood pressure. These findings have been interpreted as an additional circulatory adjustment through which the arterial blood is slowly distributed into a constricted peripheral circulation. Oxygen stores of diving animals are, in many cases, greater than those of land mammals. The blood of the seal, for example, has a higher oxygen capacity due to an increased proportion of red cells, in addition to a higher oxygen capacity of the erythrocytes themselves. The myoglobin of seal muscles also contains a larger amount of oxygen. However, increased oxygen stores would not be sufficient to account for the prolonged dives which obviously require far-reaching metabolic and circulatory adjustments. The latter involve a reduction in blood flow to the muscles. Circulation in the thighs of ducks was found decreased during diving (136). Scholander *et al.* (225) observed that the myoglobin of seal muscles is completely reduced after 5 to 10 min of a dive when the arterial blood is still half saturated (133), which indicates that the muscles were not perfused. This conclusion is also supported by the changes of lactic acid in the arterial blood, which showed a large rise after emergence from the dive but not during the dive (223). There is evidence that blood perfusion of the mesenteries and gut is also shut off during a dive. Irving *et al.* (134) noted in the seal a gradual diminishing of the diameter of the smaller arteries and veins of the mesentery during diving until they appeared bloodless.

It seems, therefore, that available oxygen is conserved for the tissues most sensitive to brief asphyxia, the heart and brain. It is well known that carbon dioxide has such an effect on the circulation, increasing cerebral blood flow while simultaneously diminishing muscular circulation. However, diving animals, such as muskrats, beavers and diving birds (ducks), show a remarkable insensitivity to CO_2 (131, 188). Irving (130) noted that the changes in cardiac action and blood pressure found in the cat upon inhalation of 10

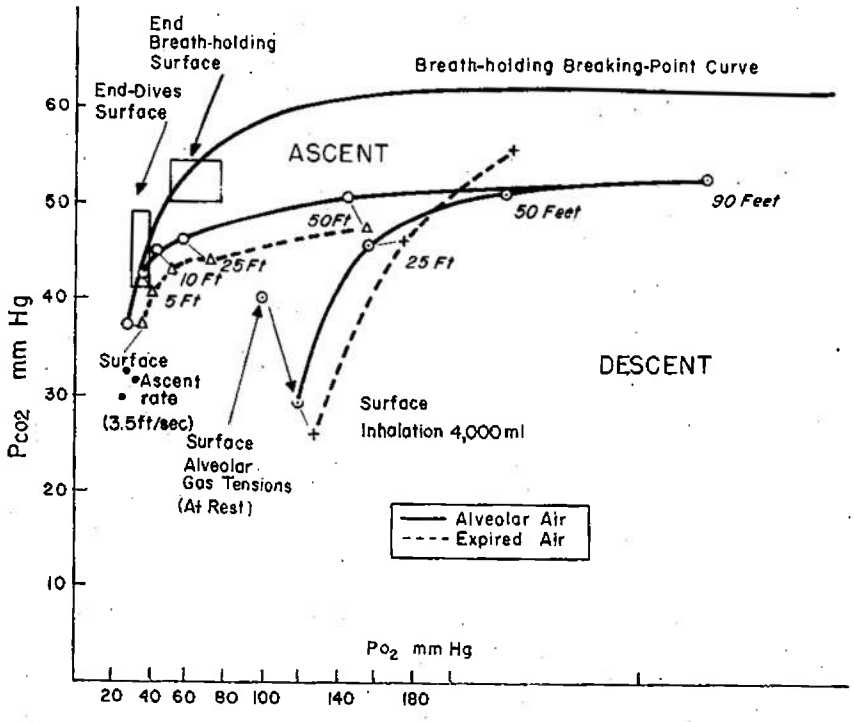

FIG. 1. Alveolar pathways during breath-holding dives to 90 feet showing reversed CO_2 gradient. At 50 feet P_{CO_2} mixed expired air is 6 mm Hg higher than P_{CO_2} "alveolar air." *Surface breath-holding breaking-point curve* drawn for comparison with *diving breath-holding curve*. End-dive alveolar P_{CO_2} decreased with increasing rate of ascent, reaching 30 mm Hg at 3.5 feet per sec. [From Schaefer & Carey (219).]

per cent CO_2 did not appear in the muskrat and beaver. Diving animals also did not exhibit the reduction in muscle blood flow which was clearly expressed in the cat. Blood flow was measured with thermoconductivity instruments in anesthetized animals. The beaver seems, however, to retain sensitivity of the cerebral circulation to CO_2. In diving animals arrest of breathing, produced by clamping of the trachea, has a very powerful effect in decreasing muscular blood flow and increasing cerebral circulation (130). They are more successful in encountering asphyxial conditions than land animals and seem to accomplish this without utilizing CO_2 as a stimulant to initiate the circulatory adjustment (130).

Metabolism studies were carried out on diving animals by comparing the pre- and postdiving oxygen consumption. The oxygen debt incurred during diving, calculated on the basis of the predive oxygen consumption, was generally larger than the excess oxygen intake after the dive. Taking into account the anaerobic and aerobic processes during diving, it was concluded that the metabolic rate during diving must have been lowered. This was found in the seal (223), the duck (3) and the American alligator (4).

Available evidence indicates that reduction in blood flow to the muscles and other tissues persists throughout the dive as a general circulation adjustment in diving animals.

CARDIOVASCULAR AND RESPIRATORY FUNCTIONS AND ADAPTATIONS IN SKIN DIVING

Schaefer and his associates (209, 219, 222) reported on physiological problems in "skin" diving (breath-hold dives) and compared the human capacity for diving with that of diving animals. Instructors at the 100-foot escape training tank, U.S. Naval Submarine Base New London, served as subjects. Alveolar pathways of O_2 and CO_2 were studied by collecting alveolar gas samples at various depths during descent to 90 feet and ascent to the surface. Due to the increase in pressure the CO_2 tension in the lungs rose quickly above the venous CO_2 tension and a reversed CO_2 gradient developed (219; fig. 1). At 90 feet, approximately 50 per cent of the predive CO_2 content of the lungs had disappeared and was taken up by the blood and tissues. The influx of carbon dioxide into the lungs during ascent appeared to be rather slow, and it was found possible to control the alveolar CO_2 level by the speed of ascent. If the ascent was fast, the alveolar CO_2 level attained on reaching the surface was low,

between 30 and 35 mm Hg CO_2; if the ascent was slow, the alveolar CO_2 tensions rose to 40 to 45 mm Hg CO_2 (fig. 1). The alveolar oxygen tension rose from control levels of 100 mm Hg to 300 mm Hg at a depth of 90 feet and on ascent fell rapidly during the last 10 feet to such low values as 25 to 30 mm Hg.

The disappearance of carbon dioxide from the lungs during dives, together with the oxygen utilization and mechanical compression of the thorax as the subject descends, produce a progressive shrinkage of the total chest volume during descent. These factors may explain the observations reported by Behnke (30) that subjects holding their breath under water increase in weight (are less buoyant).

It is reassuring to know that a diver at 90 feet is somewhat protected inasmuch as the CO_2 tension does not rise to dangerous levels and the oxygen tension is rather high. Under these conditions breath-holding time is considerably prolonged (2, 120, 209, 229). However, during the last part of ascent, or just at the moment the diver reaches the surface, available oxygen may become so depleted as to produce anoxia. The alveolar oxygen falls to a very low level at the end of ascent from dives to 90 feet. We saw one instructor become confused at the moment he gave the alveolar sample after reaching the surface, but he quickly recovered after the first breath. His alveolar O_2 concentration was 3.5 per cent. With a very low oxygen content and a normal or below normal CO_2 concentration, the nitrogen content of the alveolar air at the end of the dive is markedly increased, 89 per cent compared with a normal 79 per cent.

These findings can be explained by the difference in rate of elimination of nitrogen from that of carbon dioxide. Nitrogen, carbon dioxide, and oxygen gas tensions in the lungs are increased fourfold at a depth of 99 feet. Under these circumstances, nitrogen as well as carbon dioxide and oxygen diffuse from the lungs into the blood. Nitrogen follows the law of solubility of gases in liquids in relation to partial pressure. In carbon dioxide uptake of the blood and tissues, three factors play a role, namely, solubility in liquids, chemical combination with an alkaline buffer, and carbon dioxide transfer between the plasma and the cell system. The reservoir to take up carbon dioxide appears much larger than that for nitrogen. During ascent, which represents a form of rapid decompression, nitrogen is rapidly released from a small store under high pressure, whereas it takes longer to release carbon dioxide from a large store. On the basis of theoretical calculations, DuBois (85) has predicted

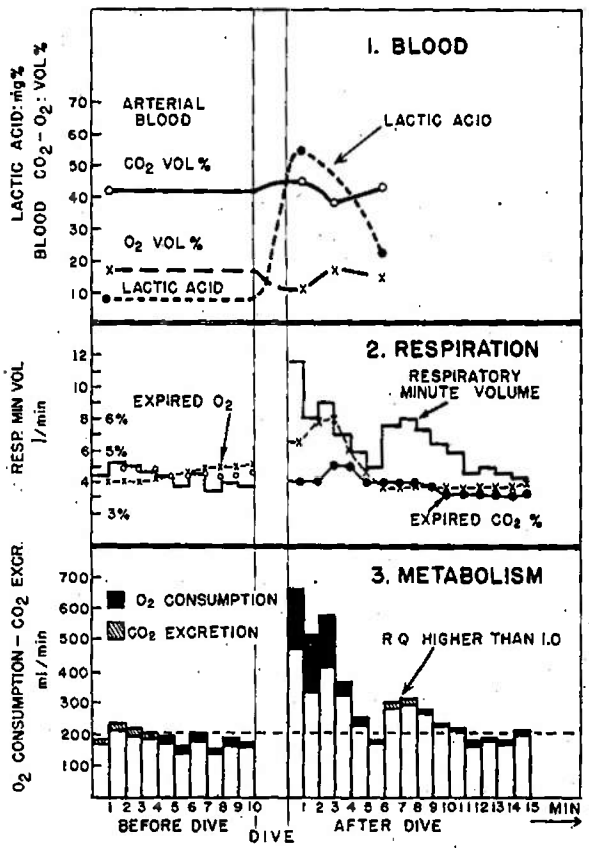

FIG. 2. Metabolism during skin diving to 90 feet.

such changes in pulmonary gas exchange during diving, and Bjurstedt & Hesser (46) confirmed the existence of a reversed CO_2 gradient during compression in dog experiments simulating skin dives to 40 m. Recently, Lanphier & Rahn (158) investigated gas exchange during simulated breath-hold dives in man and obtained similar results.

Figure 2 shows measurements of blood gases, lactic acid, respiration, and metabolism in a subject before and after a dive to 90 feet. The carbon dioxide content of the blood rose very slightly while the oxygen content fell during the dive. The lactic acid content rose from a control value of 9 mg per cent to 55 mg per cent 1 min after the dive and decreased to 25 mg per cent within 5 min. On more frequently collected venous blood samples, peak lactic acid concentrations were measured after 3 min of recovery following the dive. The 1 min values were consistently lower than the 3 min values. This corresponds with the findings recently obtained by Scholander *et al.* in pearl divers (224).

In a control experiment in which one of the pearl divers swam at the surface, producing approximately the same degree of work as in diving, hardly any change in blood lactate was found. This suggests that the delayed but large rise in lactic acid found during the recovery phase after diving in man, which is quite similar to that observed in the seal, might also be interpreted as an indication of reduced muscle blood flow during the dive. Scholander also noted a marked diving bradycardia during active diving. The pulse rate is reduced to one-half of the predive value, while breath holding at the surface leads to a much smaller decrease in pulse rate. Extra systoles were noted in ECG tracings during the dive, and arrhythmias and atrial fibrillation during the recovery phase. Blood-pressure measurements made after breath holding under water and in air did not show significant changes in systolic and diastolic pressures (224).

Some observations were made in studies on skin diving which have a bearing on the question of bubble formation in decompression sickness. In four experiments, arterial and venous blood samples were drawn before and after the dive. It was noted that the first 2 ml of arterial and venous blood drawn immediately after the dive had a foamy appearance; in the following 2 ml the foam had disappeared. Since neither the alveolar carbon dioxide nor the blood carbon dioxide was increased in samples obtained during the first 30 to 40 sec and, because of the quick release of nitrogen from small stores (physical solution), it was concluded that the foam on the first 2 ml of blood consisted of nitrogen. The conditions under which this "silent" bubble formation, not leading to symptoms, occurred were: a decompression ratio of 3 to 1, a rate of ascent of 3 feet per sec, and work during ascent (climbing up a line). Interpretation of these findings as silent bubbles is in agreement with the view of Bateman (16) that the decompression ratio at which bubbles occur may be far below the symptom threshold.

In some aspects adaptation of skin divers is similar to that of diving animals. Skin divers, for example, show an insensitivity to CO_2 and to low O_2 also. The high tolerance to CO_2 is developed during the diving period and lost after a 3-month layoff period as shown in CO_2 sensitivity tests on eight tank instructors (215). 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 (215). They consisted of a decrease in pH, an increase in P_{CO_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 3-month layoff period (215). Furthermore, evidence of an increase in CO_2 stores as the result of diving was obtained in instructors following a 2-year period of water work when compared with data obtained after a 3-month layoff period (83). Under the first condition, end-tidal CO_2 tension was significantly elevated and more CO_2 was eliminated from the body CO_2 stores during a 1-hour period of constant hyperventilation.

In respect to lung volumes, skin divers show a unique form of adaptation not previously noted in diving animals. Longitudinal studies carried out on instructors at the escape training tank, U. S. Naval Submarine Base New London, after 1 year of duty showed an increase in vital capacity, inspiratory reserve, tidal volume, and total lung capacity associated with a decrease in residual volume (60). Since a large tidal volume, a small respiratory rate, and large lung volumes were implicated in the development of a low response to CO_2 (211), the adaptive changes in lung volumes of divers might well contribute to their reduced sensitivity to CO_2. Another result of this adaptation in lung volumes is the extension of the maximum safe depth to which the diver can go (see below). Similar results on lung volumes and respiratory pattern, correlated with lowered response to carbon dioxide, were obtained by Miles (179) in a group of 100 divers, both conventional and free-swimming.

HAZARDS OF DIVING AND RELATED ADAPTIVE CHANGES

In recent years a great many people have taken up the sport of skin diving to carry out spear fishing, underwater photography, and the like. They may wear face masks and snorkels, but their activity is limited by their ability to hold their breath and their endurance as swimmers. With the development of the aqualung, an open-circuit demand type unit, sport diving has become possible and depths of about 150 feet can be reached, depths to which formerly only professional divers in conventional diving outfits were able to descend. The self-contained underwater breathing apparatus (scuba) diver, who can stay under water for a considerable time, is exposed to certain hazards which are also common in conventional dives with suit and helmet, such as barotrauma, nitrogen narcosis, oxygen toxicity, air embolism, and

decompression sickness (156). These topics are discussed separately below. The scuba, deep-sea, and skin diver are all subject to the effects of unequalized pressure differences across the air-containing structures, middle ears, sinuses, lungs, and gastrointestinal tract. If a swimmer or diver cannot equalize pressure in the middle ear during descent due to a blockage of the eustachian tube, he will experience pain and on further descent may rupture the eardrum. If this happens in cold water, vertigo and nausea result due to caloric vestibular stimulation. This is a serious hazard since the diver may become completely disoriented. If the sinuses do not equalize during descent, trauma of the lining membrane with transudation and hemorrhage can develop.

The Thoracic "Squeeze"

The skin diver who holds his breath during descent will begin to experience some pressure in his chest when he reaches a certain depth. The air in his lungs is more and more compressed to a smaller volume, a process which can be compared with an exhalation. When the total air in the lungs is compressed to the volume equal to the residual lung volume plus the volume of the airways, the threshold for the thoracic "squeeze" is reached. Measurements of the ratio of total lung capacity to residual volume in instructors at the escape training tank indicated that this threshold for these subjects was reached at about 85 feet (215). However, such a number for maximal depth cannot be generalized since lung volumes differ greatly among individuals. If the diver descends beyond this point, thoracic squeeze may develop with pulmonary edema and hemorrhage. The squeezing force is a pressure differential between the blood and extracellular fluid on the one hand and the tissue of air-containing space on the other. Cases of thoracic squeeze encountered in skin diving are usually not severe. Adaptive changes in the lung volumes, noted in the tank instructors after 1 year of duty, produced an increase in the ratio of total lung capacity to residual volume plus volume of airways, resulting in an extension of the threshold for the thoracic squeeze from 85 feet to 105 feet (215).

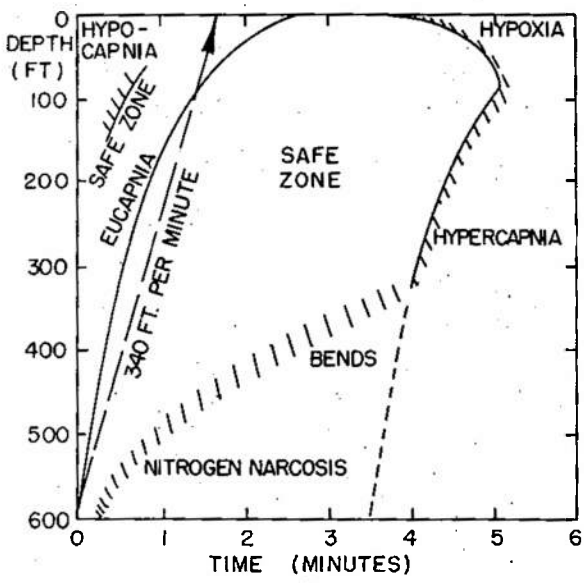

FIG. 3. Depth-time curve for buoyant ascent (submarine escape). [From DuBois *et al.* (86).]

CARBON DIOXIDE INTOXICATION AND ADAPTATION IN DIVING

Skin Diving

During skin diving CO_2 intoxication is less likely to occur than in scuba diving. The studies of the alveolar pathways during dives to 90 feet, mentioned above, demonstrated that carbon dioxide is taken up by the tissues in a kind of pressure filling and that the levels of alveolar and blood CO_2 are rather low throughout the dive and can easily be controlled with the speed of ascent. A lowered sensitivity to CO_2 was established in skin divers as part of regular adaptation (215) enabling the diver to stay longer under water. However, this advantage might be compensated by the increased danger of hypoxia during the last part of ascent following a prolonged dive.

Submarine Escape (Free and Buoyant Ascent)

Buoyant ascent (aided by an inflated life jacket) has been successfully carried out from depths of 300 feet at an ascent rate of 340 feet per min without respiratory distress (50). Recent evaluation of alveolar gas exchange data obtained during buoyant ascent from 90 feet have shown that the alveolar CO_2 tension can be kept at normal levels at the average ascent rates used (86). A theoretical depth time curve for buoyant ascent was established, according to which it appears possible to make these ascents from 600 feet without being endangered by CO_2 narcosis, nitrogen narcosis, or anoxia (fig. 3).

Scuba Diving

Several cases of unexplained loss of consciousness were observed with the use of oxygen closed-circuit diving equipment in which canisters are employed for CO_2 removal (15). Carbon-dioxide intoxication was implicated as the most likely cause of the "shallow-water blackout." Additional investigations demonstrated that it is possible in most subjects to produce a marked carbon-dioxide intoxication without severe respiratory dyspnea. In other words, the depressant effects of carbon dioxide could manifest themselves without the warning sign of a strong respiratory stimulation. Predominance of depressing CO_2 effects over respiratory stimulation was facilitated by physical exertion and high oxygen tensions. However, Miles (178) has pointed out that shallow-water blackout might be caused by sudden increases in oxygen tensions leading to oxygen syncope. When an open- or a closed-circuit scuba is used at greater depth, the direct effect of pressure produces an increased density of the breathing mixture resulting in increased resistance to breathing. Under these conditions the work of breathing was found to be increased by the resistance developed in the breathing apparatus and in the airways of the diver (170, 173). Pulmonary resistance at 4 atm pressure increased twofold compared with the values at sea level (174). Froeb (96) compared the respiratory response to CO_2 in 16 professional divers using scuba equipment with those of nondivers 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 unit, a higher mean and tidal P_{CO_2} tension was found in the trained swimmers during swims at a speed of 1.1 to 1.8 km per hour (106, 107). Under resting conditions under water, differences in end tidal P_{CO_2} were negligible. Findings indicated some degree of adaptation to CO_2 in the trained swimmers which perhaps in part was related to the noted respiratory pattern with long postinspiratory pauses. Furthermore, adaptation to increased work of the inspiratory muscles might have contributed to the elevated P_{CO_2} in the trained underwater swimmer because it was shown that alveolar P_{CO_2} increases linearly with the workload on the inspiratory muscles (181).

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 the accumulation of CO_2. Often, this might 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 CO_2 retention during underwater work (152, 153). The respiratory minute volume declined during work dives to moderate depth using oxygen-nitrogen mixtures. The degree of retention of carbon dioxide was related to the ventilatory response to CO_2 (154). Those with a high tolerance to CO_2 retained more carbon dioxide. When breathing resistance was reduced by the use of helium-oxygen mixtures, the carbon dioxide retention was small or absent. A lowered sensitivity to carbon dioxide was frequently found in these divers (157).

Nature of CO_2 Adaptation

Respiratory adaptation during prolonged exposure to 3 per cent and 1.5 per cent CO_2 consists of lowered ventilatory response to increased CO_2 concentration which was found to be associated with a respiratory pattern of larger tidal volume and reduced respiratory rate (208, 213). Simultaneous acid-base balance studies indicated that respiratory adaptation is correlated with the compensation of the respiratory acidosis induced by CO_2 inhalation (213). The two phases of acidosis are associated with a period of excitation followed by a period of depression of the central nervous system and the autonomic system (59, 214).

The CO_2 effects on the central nervous system have recently been reviewed (216). It has been demonstrated that during CO_2 exposure stimulatory effects on the hypothalamic cortical system are associated with simultaneous depressing effects on the cerebral cortex. The latter represents a direct action of CO_2. After adaptation to carbon dioxide, the stimulatory effects on the autonomic system decrease and the cortical depressive effects become dominant. Furthermore, the stress effect of CO_2 (increased adrenal cortical activity) was found to be restricted to the period of uncompensated respiratory acidosis (212).

Evidence of circulatory adaptation of CO_2 was found in a decrease in pulse rate (208) and a marked prolongation of the time required for the pulse rate and the systolic and diastolic blood pressure to return to the initial level after exercise (51). Since the divers

are only intermittently exposed to CO_2, the question arises as to whether one can speak of CO_2 adaptation under such circumstances. It is known that brewery workers who are intermittently exposed to 3 to 4 per cent CO_2 show significant increases in blood bicarbonate and a reduced respiratory response to CO_2. Furthermore, it was reported that a 9-day intermittent exposure following a 6-day continuous exposure to 3 per cent CO_2 did not change the state of adaptation reached during the first part of the experiment (208). These findings seem to indicate that intermittent exposure to CO_2 also produces adaptive changes.

ANOXIA

A real danger of anoxia exists during skin diving since the oxygen content falls rapidly during the last 10 feet of ascent (just before reaching the surface). The end-dive alveolar oxygen tensions of 25 to 30 mm Hg clearly indicate the hazard of anoxia which may lead to unconsciousness. The practice of many skin divers to prolong the breath-holding time under water by hyperventilation or oxygen breathing prior to the dive will exaggerate the danger of anoxia. In a recent paper, Craig (68) also emphasized that among the causes of loss of consciousness during underwater swimming hypoxia is probably the most important factor. Some measure of adaptation to hypoxia appears to be associated with adaptation to CO_2 in divers. Commensurate with a reduced respiratory response to CO_2, a lowered respiratory response to inhalation of 10.5 per cent O_2 in N_2 was observed (220). Moreover, as compared to untrained subjects, these subjects contracted a much larger O_2 debt during exposure to a hypoxic gas mixture (218).

COMPRESSION

In diving operations and in caisson work, man is exposed to compressed air. A large number of investigations have been carried out to determine the causes of compressed air illness and decompression sickness [see Behnke (27)]. However, the numerous factors with distinct physiological effects operating in the high-pressure environment present great difficulties in the way of experimental design and clear analysis. Effects of acute changes in pressure were frequently considered as direct effects of pressure. Effects of hydrostatic pressure (submergence) are absent in the dry pressure chamber. Several explanations have been proposed for the effects of compressed air. Since increased pressure per se alters the viscosity of gases and their diffusion, these physical changes are considered to contribute to the effects of increased pressure. Case & Haldane (61) emphasized the increased work of breathing resulting from the increased density of gases under higher pressures. On the basis of large experimental material, Bert (43) concluded that the effects of increased pressure were caused by increased oxygen tensions, so he then used compressed air to study oxygen poisoning. This view was widely accepted. However, Hill & Macleod (123) and Orzechowski & Holste (189) demonstrated that the effects produced by increased oxygen tensions in compressed air are more severe than those obtained by the same oxygen tensions using pure oxygen. One reason is that nitrogen or another inert gas has to be present in the lungs to prevent atelectasis formation due to absorption of oxygen (194). Nitrogen itself has been shown to produce central nervous system effects if the air pressure increases above 100 to 150 feet.

Cardiovascular Effects of Increased Pressure

The earlier notion that increased pressure produces a direct mechanical squeeze effect on the peripheral blood vessels (182, 233) was disproved in experiments by Oliver (187) and Hill & Macleod (121, 123). According to Bert (43), increases in blood pressure and pulmonary capacity observed in animals exposed to raised atmospheric pressure were caused by mechanical effects of the increased pressure on the abdomen and diaphragm.

Increases in vital capacity in man and animals exposed to high pressures have been observed in more recent investigations (122, 229). There is general agreement that the pulse rate decreased under increased pressure, whereas findings on blood pressure vary so much that no definite statement is possible.

Data on pulse rate, systolic blood pressure, and pulse pressure obtained by Shilling *et al.* (230) on a group of 31 men tested at atmospheric pressure and 2, 4, 6, 7 and 10 atm showed a slight decrease with increasing pressure. Furthermore, the Schneider index score was found increased and cardiac minute volume was decreased by about 1 liter at 6 atm. Slight increases in blood pressure were observed in men subjected to 2 atm by Javal (135). Retinal blood vessels were found to be contracted and anemic in subjects exposed for 1 hour to 1087 mm Hg pressure (248).

Studies on caisson work did not show any significant changes in vital capacity or pulse rate as the result of 6 months work in caissons (202). Brooks (55) did not find any changes in the arterial blood pressure of 75 men who had worked in caissons from 1 month to 5 years. Hornung (128) demonstrated that the heart size of caisson workers increased commensurately with the rise of pressure in the lock, and decreased slightly after a pressure equilibrium was established but without returning to the control value. According to Marquort & Rietz (169), the electrocardiogram in men exposed to increased pressures indicated a change in the position of the heart due to lowering of the diaphragm. No pathological changes were noted in the ECG of caisson workers after years of activity. This is in contrast to findings of Breu (54) who observed in 41 per cent of 120 caisson workers high positive T waves which were considered as evidence of myocardial damage. The changes in T waves are similar to those found after oxygen inhalation (see below). Available literature does not contain any reports about adaptive circulatory changes in caisson workers.

OXYGEN TOXICITY

The effects of increased partial pressures of oxygen at atmospheric pressure are treated separately from those of increased oxygen tension in excess of 1 atm since one of the forms of oxygen poisoning, oxygen convulsions, occurs only under the latter condition. This subject has been reviewed by Bean (18) and Matthes (172).

Oxygen Effects at One Atmosphere

Inhalation of oxygen concentrations above 65 per cent corresponding to a Po_2 higher than 530 mm Hg has deleterious effects in most warm-blooded animals and leads eventually, after days or weeks, to death. Comroe *et al.* (66) were able to establish the threshold oxygen tension and also the time of onset of symptoms due to oxygen toxicity by exposing a large number of healthy young subjects to 10, 50, and 75 per cent O_2 for 24 hours. Up to 12 hours, 100 per cent oxygen could safely be inhaled, but after 24 hours of oxygen breathing symptoms of substernal stress were noted in 86 per cent of the subjects. Inhalation of 50 per cent oxygen induced no symptoms during 24 hours. However, a decrease in vital capacity was found after 24 hours of exposure to 100 and 50 per cent oxygen. The alveolar oxygen tension under the latter condition is approximately 300 mm Hg. A reduction in vital capacity after prolonged exposure to increased oxygen tension was also reported by Clamann & Beeker-Freyseng (64) and Michel & Langevin (177). The latter exposed subjects for 7 days to an altitude of 10,000 feet with an oxygen partial pressure of 410 mm Hg corresponding to 55 per cent oxygen at sea level.

There is ample evidence that breathing oxygen or hyperoxygenated gas mixtures results in a slowing of the heart rate (5, 40, 84, 175). The threshold for the bradycardia effect is 50 per cent which corresponds to an alveolar Po_2 of 300 mm Hg. This slowing of the heart rate was not observed in subjects breathing an air mixture containing less than 50 per cent (176). The magnitude of the response was proportional to the oxygen concentration in the inhaled air mixture. The fall in pulse rate amounts to 3 to 10 per cent of the initial value and is of a transitory nature. After 20 min the pulse rate rises again and reaches control values after 50 min of oxygen breathing (6, 176).

The immediate decrease of pulse rate and respiratory minute volume upon inhalation of pure oxygen suggested a tonic activity of the chemoreceptors at normal oxygen tensions (84). This was definitely established by Dejours *et al.* (76) who also found that this chemoreceptor O_2 drive of respiration disappears above an alveolar oxygen tension of 170 mm Hg. The bradycardia is apparently caused by stimulation of the vagus. Administration of atropine prevents the decrease of heart rate produced by inhalation of pure oxygen at atmospheric pressure (1).

Cardiac minute volume and stroke volume are both reduced during oxygen breathing. Reported decreases in the cardiac minute volume amounted to 10 to 20 per cent and those of the stroke volume were only 6 to 7 per cent (5). Since the total oxygen consumption did not change, findings indicate that oxygen utilization is increased under these conditions. Similar results were obtained by Whitehorn *et al.* (250) who also pointed out that maintenance of the arterial blood pressure level, in spite of a reduced cardiac output, might be interpreted as evidence of an increase in general peripheral vascular resistance. Coronary vessels appear to constrict on administration of oxygen and a decrease of 15 per cent in coronary blood flow was found in dogs (91). No change in cardiac output was observed during breathing of a 45 per cent oxygen mixture; this corresponds with the results of Meda on pulse rate (203).

According to older studies the blood pressure in man did not seem to be affected by inhalation of oxygen. More elaborate investigations of the circulatory effects of oxygen breathing in normal man were very recently reported by Daly & Bondurant (71) who demonstrated unequivocally that O_2 breathing increases systemic resistance and blood pressure. Furthermore, it was found that the oxygen-induced decrease in heart rate and rate dependent decrease in cardiac output persist in the circulatory response to reactive hyperemia, which seems to indicate a reflex effect of hyperoxia.

There is some evidence that increased oxygen causes a reduction in cerebral blood flow. Quantitative studies of cerebral circulation in man showed that 50 (129) and 80 per cent (244) oxygen in the inspired air have negligible effects, whereas inhalation of 85 and 100 per cent oxygen cause a slight reduction of cerebral blood flow (approximately 12 to 15 per cent) (142, 147). This rather small effect on cerebral circulation is not significantly increased when the ambient pressure is raised to 3.5 atm, probably because of associated hypocapnia (147).

The effects of increased oxygen tension on the electrocardiogram consist of a flattening of the P wave and an increase in the amplitude of R and T. Enlargement of the T wave is particularly pronounced in heart patients after oxygen inhalation. Pathological waves may become more distinct after oxygen inhalation. The time intervals of PQ, QRS, and QT are usually not changed. Prolonged PQ intervals and lowered ST segments were found to be normalized after oxygen breathing (6, 14, 175).

Oxygen Paradox

If a person is in a hypoxic state and suddenly has pure oxygen to breathe, his condition may deteriorate and he may become unconscious for up to 30 sec. This effect of oxygen was first noted in studies involving rapid recompression from simulated altitude. The term oxygen paradox was coined by Ruff & Strughold (206) in 1939. Latham (160) carried out experiments on 52 subjects who were first made anoxic by inhaling air for 4 to 5 min at 20,000 feet of simulated altitude and then given pure oxygen. Of the 52 subjects, 13 (25 per cent) showed symptoms. After 12 sec of oxygen inhalation, errors in writing tests reached a peak indicating that CNS disturbances are the first manifestations of the oxygen paradox reaction. Cardiovascular responses followed 40 sec later and were associated with muscular incoordination. Somewhat later, signs of impending cardiovascular collapse developed, commensurate with a rapid fall in systolic blood pressure and an increase in peripheral blood flow. It is possible that the neurological manifestations of the oxygen paradox reaction are the consequences of an impairment of cerebral circulation. The paradox reaction does not occur if oxygen is administered slowly.

Oxygen syncope was studied by Miles (178) in 36 young adult shallow-water divers, all experienced in the use of breathing apparatuses. He developed a test in which he incorporated the "stress conditions" frequently encountered in underwater swimming, such as sudden increases in intrapulmonary pressure (blowing against a nose clip), breath holding, and sudden changes in oxygen concentrations in the breathing unit.

It was found that the threshold for oxygen syncope is lowered by inhalation of oxygen even at normal barometric pressure. Miles concluded that under conditions of increased pulmonary pressure, combined with peripheral vascular pooling, inhalation of a gas mixture containing increased oxygen tensions is more likely to produce syncope than breathing air. The incidence of nausea, dizziness and weakness was also much greater in subjects after inhalation of oxygen when compared with air breathing. Findings were explained on the basis of the cerebral vasoconstriction effect of oxygen.

Effects of Oxygen in Excess of One Atmosphere

Inhalation of oxygen at a pressure of approximately 2 atm after sufficient time will result in generalized convulsions. With increasing depth the toxic manifestation of oxygen becomes greater and occurs after shorter exposure times (80, 81, 255). Oxygen convulsions have been reported at a pressure as low as 33 feet of sea water (80). Practical use of oxygen breathing has been considered to be limited to 30 feet (255) or 25 feet (80). Even these narrow limitations underrate the recognized danger of oxygen breathing while under water. Working while under water will reduce the tolerance to oxygen markedly. Prodromal signs and symptoms listed in the order of their percentage of incidence during underwater exposure include vertigo, nausea, lip twitching and other involuntary tremors, drowsiness and disorientation, acoustic hallucinations, and paresthesia (81). These findings were obtained in a study of a large number of exposures to high oxygen pressures in a wet chamber. Symptoms of pulmonary irritation were not seen because nervous

symptoms forced termination of the experiments before pulmonary symptoms could develop. However, in studies of oxygen toxicity in underwater swimming, in which 14 out of 50 exposures (28 per cent) were terminated due to toxic manifestations, dyspnea was by far the most frequent symptom (210). The subjects complaining about dyspnea had a very rapid respiratory rate (mostly above 32) and reported a resistance to breathing and inspiratory inhibition.

The differences appear to be related to the different effects of oxygen breathing on respiration in rest and exercise. Under resting conditions, oxygen breathing increases respiratory minute volume at normal atmospheric pressure (9), and even more at 3.5 atm (151). Respiratory rate remains unchanged while tidal volume increases. However, oxygen inhalation causes a reduction in pulmonary ventilation during moderately strenuous exercise (8) which has been explained as a predominance of the depressive effect of oxygen on the respiratory center. Since oxygen breathing in underwater swimming produces a strong parasympathicotonic stimulation, as indicated in pulse rate measurements, symptoms of pulmonary irritation and inspiratory inhibition might be caused by excitation of the vagal inhibitory reflex (210). The average pulse rate measured at the beginning of 3-min rest periods after each 15 min of underwater swimming showed a consistent decline with continuing exercise, falling even below the initial resting values at the end of 93 min. The cardioinhibitory action displayed under these conditions led eventually to a fixation of pulse rate, e.g., the differences between exercise and rest disappeared. This sign preceded the development of symptoms in 78 per cent of the cases and can therefore be used as a warning sign. Manifestations of symptoms were associated with strong increases in pulse rate and respiratory rate.

Two cardiovascular findings during exposure to increased percentage of oxygen at 1 or more atm seem to be well established: the bradycardia which is of vagal origin (1, 25, 71), and the increase noted in pulse rate and blood pressure if symptoms of oxygen toxicity develop in man (32, 33, 40, 255). The reported fixation of pulse rate (210) appears to denote the end point of the predominant parasympathetic activity and the approaching release of increased sympathetic activity which is associated with symptoms of oxygen toxicity. Exposure to increased O_2 tension results in a decrease of erythrocytes and hemoglobin (5). Hemopoiesis, which is also known to increase during adaptation to high altitude, appears to be influenced by the relation between O_2 utilization and O_2 supply.

A theoretical toxicity curve for time and depth of exposure to oxygen was developed for conditions of underwater work or swimming. This proposed oxygen limit curve was tested with 19 subjects working under water at various depths while breathing oxygen (152). Although the theoretical oxygen toxicity curve proved to be acceptable as a general guideline, symptoms of oxygen toxicity were occasionally experienced within a depth-time range designated as safe (87).

Oxygen inhalation by human subjects at 3 atm in a dry compression chamber was well tolerated for 3 hours. During the 4th hour, however, symptoms of dizziness and nausea developed (31). Impending collapse was always signalized by an increase in pulse rate and rise in systolic and diastolic pressure. These findings correspond with those reported by Schaefer (210) in studies of underwater swimming. Furthermore, rapid contraction of the visual field and failure in visual acuity were observed. After transition to air, nausea and dizziness disappeared within a few minutes, whereas the recovery of cardiovascular functions required a considerably longer time.

Many studies have been carried out in the past to determine the cause of oxygen convulsions (18). A direct toxic effect of oxygen at high pressures upon brain cells, carbon dioxide autointoxication due to the breakdown of the hemoglobin transport function for carbon dioxide (104), and vasoconstrictor effects of high P_{O_2} (73) have been considered as mechanisms involved in the development of oxygen toxicity.

When oxygen is inhaled at 3.5 atmospheres pressure, the blood contains 6.5 vol per cent oxygen in physical solution. This amount would be sufficient to cover the oxygen supply of most tissues since the O_2 deficit of the mixed venous blood is only 5 vol per cent and even in the brain circulation is not more than 6 vol per cent. One would assume, therefore, that the oxygen bound on hemoglobin would not be utilized and that venous and tissue partial pressures of oxygen would be greatly increased during exposure to 3.5 atm of oxygen. However, Lambertsen *et al.* (147) demonstrated that under these conditions jugular venous hemoglobin was still somewhat reduced (venous Hb O_2 saturation 89 per cent), even though arterial oxygen tensions reached a level of nearly 2100 mm Hg.

The effect of the change in atmospheric pressure was to reduce the cerebral blood flow by 25 per cent and increase the vascular resistance of the brain by 55

per cent. The reduced flow resulted in a small increase in the arteriovenous volume difference. When the arteriovenous difference is thought of as a tension difference, the figure is very large (about 2000 mm Hg). This is, of course, due to the oxygen's being in solution rather than in combination with hemoglobin.

The observed increase in central venous P_{CO_2} of 3 mm Hg was apparently sufficient to stimulate respiration which, in turn, resulted in a 5 mm Hg decrease in arterial P_{CO_2}, raising the arteriovenous difference to 8 mm Hg. Lambertsen *et al.* (147) consider arterial hypocapnia as the cause of the cerebral vasoconstriction produced by inhalation of oxygen at high pressure since this vasoconstrictor effect could be eliminated by the addition of 2 per cent CO_2 to the oxygen. Under these conditions arterial P_{CO_2} was maintained at normal levels, while venous P_{O_2} rose approximately 1000 mm Hg (146, 148).

Since the enhancement of oxygen toxicity by carbon dioxide breathing was found to be caused by a large increase in mean brain capillary oxygen tension due to CO_2-induced vasodilation, it was reasonable to assume that the reduction in oxygen tolerance by exercise would have a similar origin. However, in recent experiments in which subjects carried out exercise (workload 745 kg-min) while breathing oxygen at 2 atmospheres pressure, Lambertsen *et al.* (149) demonstrated that the postulated hypercapnia and large increase in oxygen tension did not occur. Although the arterial P_{O_2} rose under these conditions to 1200 mm Hg, the internal jugular venous P_{O_2} increased only from 33 mm Hg at rest to 61 mm Hg during exercise while the level of jugular venous P_{CO_2} was elevated 6.5 mm Hg. The findings of the Lambertsen group have brought additional evidence that oxygen inhalation at high pressure interferes with the hemoglobin transport function for carbon dioxide, and they refute the theory of carbon dioxide autointoxication as the cause of oxygen convulsions. If the venous P_{CO_2} is considered an index of the tissue P_{CO_2} tension, the observed increase of 3 mm Hg rules out any significant elevation of tissue CO_2 tension, which is in agreement with earlier work of Behnke *et al.* (36) who found a rise of 6.5 mm Hg in the mixed venous blood of dogs exposed to 3.8 atm of oxygen.

The theory of carbon dioxide autointoxication was mainly supported by observations of high tissue CO_2 tensions (between 200 and 300 mm Hg) in intraperitoneal and subcutaneous gas pockets of small animals exposed to high oxygen pressures (58, 226, 241, 242). However, more recent experiments with rabbits, cats, and dogs, in which the same technique was used, demonstrated that the rise of tissue CO_2 tension during exposure to high oxygen pressure is associated with respiratory failure of terminal hyperoxia (150). Furthermore, in experiments with high O_2 pressure, CO_2 excretion was found increased only after the onset of generalized convulsions; this was interpreted to mean that CO_2 retention is the consequence and not the cause of convulsions (246).

Evidence so far indicates that interference with the carbon dioxide transport function of the blood in hyperoxia cannot be considered to be the cause of convulsions. It appears, therefore, more likely that the cerebral symptoms of oxygen toxicity are produced by direct effects of high oxygen tensions. High oxygen pressure depresses tissue respiration in vitro, and brain tissue appears to be more susceptible to the action of oxygen than other tissues (237, 238). However, the time required for oxygen to depress tissue respiration was much longer than the latent time of convulsions at comparable pressures in animals (79).

In view of the existing large gradients of oxygen tension from the arterial to the venous side, it has been proposed (147) that the cells at the arterial capillary end, where much higher oxygen tensions exist comparable to those producing irreversible poisoning of glucose oxidation in tissues, are affected by oxygen and act as trigger mechanism for the development of generalized convulsions. In any case, the subtle derangements of enzyme activities responsible for the in vivo toxic effects of oxygen still await elucidation.

Neurophysiological studies of oxygen toxicity demonstrated that electroencephalographic tracings during oxygen convulsions cannot be distinguished from those obtained in grand mal epilepsy (161) and that the seizures appear during or just after a sharp rise in cerebral oxygen tensions as measured with the platinum electrode (21).

Investigations of Noell (185, 186) on the effect of increased oxygen tension on the visual cell of the rabbit retina demonstrated that oxygen exerts on the visual cell a direct toxic effect which is cumulative. Noell (186) pointed out that in its cumulative action oxygen poisoning resembles the effects of X-irradiation, which observation supports the theory advanced by Gerschman *et al.* (102) that oxygen poisoning and X-irradiation have one common mechanism of action, namely, the formation of oxidizing free radicals. It has been demonstrated that the lethal effects of

X-irradiation are enhanced by high oxygen and reduced by anoxia. Furthermore, agents which gave a protection against X-irradiation, such as glutathione and cysteine, also afford a protection against oxygen poisoning (102). It is reasonable to assume that oxidizing free radicals such as $HO\cdot_2$, $OH\cdot$, and H_2O_2 would react rapidly and perhaps initiate chain reactions.

Under these circumstances the body does require antioxidant defenses against uncontrolled oxidations (100). Differences in the available antioxidant defenses might account for the wide variety in species and organ susceptibility. Clarification of the mechanism of action through which substances protect against oxygen toxicity is significant for the progress in this field. For example, it has been shown that cobalt, which is known to destroy hydrogen peroxide (101), also protects mice against 1 atm of oxygen. The action of toxic oxidizing free radicals does not require postulation of an O_2 vasoconstrictor effect on the blood vessels or any specific changes in acid-base parameters. The theory may, therefore, offer an explanation for conditions, such as exercise at high P_{O_2}, in which changes in circulation, arterial, and venous P_{CO_2} and P_{O_2} are too small to account for the reduction in oxygen tolerance.

Pathological Changes Induced by Oxygen

Exposure to oxygen tensions above 500 mm Hg produce, after 12 to 14 hours, pathological changes which are particularly expressed in the lungs in all warm-blooded animals. Outstanding features of the acute and subacute pulmonary oxygen effects at normal and higher barometric pressures are increased permeability of the pulmonary blood vessels with hemorrhages and edema, swelling and desquamation of the alveolar epithelium, and fibrin formation resulting after a few days in fibrinous bronchopneumonia (44, 65, 138, 139). Unilateral and bilateral vagotomy did not produce any marked differences in the pulmonary pathology of animals exposed to approximately 600 mm Hg of oxygen tension (168). In rats exposed to 720 to 750 mm Hg of oxygen tension (total pressure, 1 atm), a massive pleural effusion was found as the cause of death (53). Myocardial damage was observed in mice as the result of high O_2 pressure (140). Later changes during prolonged exposure to increased P_{O_2} involve hyperplasia and degenerative changes in the alveolar cells (235), thickening and hyalinization of pulmonary arterioles (41), and dilatation of the right side or of both sides of the heart (41).

Experimental investigations of pulmonary effects of oxygen carried out at higher oxygen tensions (between 1500 and 2500 mm Hg) show augmentation of the pulmonary pathology which also develops at an earlier time. However, under these conditions a strong neurogenic component is present since most of the animals have convulsions prior to the onset of pulmonary changes. In addition, hormonal factors contribute in large measure to the development of histopathological effects.

Exposure to high oxygen tensions produces a typical stress reaction with increased activity of the pituitary adrenal system (22, 23, 103). Hypophysectomy (26) and adrenalectomy (103) give protection against the noxious effects of oxygen, whereas cortisone and adrenaline injection (24) facilitate the toxic oxygen effects. These findings demonstrate the involvement of hormonal factors and stimulation of the sympathetic system in the development of oxygen-induced pulmonary damage, although the mechanisms of action are not clear. It should be kept in mind that airway resistance is decreased under stress conditions. On the other hand, diffuse atelectasis has been found in small animals exposed to increased oxygen tensions as a result of absorption of oxygen from nonventilating alveoli (194).

Acclimatization to Oxygen

During prolonged exposure to oxygen, a crisis develops during the first days in which a number of animals die while others recover and continue to live for longer periods (234). This is quite similar to findings obtained under conditions of chronic CO_2 exposure (213). Smith *et al.* (235) provided histological evidence for pulmonary adaptation in rats which survived 72 days' exposure to 80 per cent oxygen (total pressure, 1 atm). The adaptive pulmonary changes consisted in greater cellularity and thickness of the alveolar wall and hyperplastic alterations of the pulmonary capillaries. These adapted animals showed no signs of O_2 poisoning when they were re-exposed to the same conditions of 560 mm Hg O_2 in compressed air. It was concluded that the increased resistance to oxygen was based on chronic changes in the pulmonary epithelium. Measurement of pulmonary arterial pressure was obtained under similar experimental conditions in which rats were exposed for 4 to 6 weeks to 4 atm pressure (O_2 tension ranging from 532 to 760 mm Hg) (41). Pulmonary hypertension noted after 24 days of exposure was caused by the development of obliterative vascular changes. These

appeared first in the pulmonary arterioles (thickening and hyalinization) and were followed later by degenerative lesions in the large pulmonary arteries. The right ventricle was found enlarged and the systolic pressure decreased. No pathological changes were seen in the systemic circulation. The reported "adaptive pulmonary changes" observed in chronic O_2 toxicity studies with compressed air were certainly influenced by the presence of nitrogen which reduces atelectasis formation and probably mortality (194).

However, Barach *et al.* (13) found that rats, which usually die after 3 to 4 days in 100 per cent O_2, developed an increased tolerance to 100 per cent O_2 within a period of 6 to 12 days after intermittent exposure to oxygen with four 15-min intervals on air per day. This adaptive response could not be explained by chronic morphological changes of the pulmonary tissue. Rabbits could not be adapted to high concentrations of oxygen by gradually increasing the oxygen concentrations from 21 to 85 per cent (11). The technique of intermittent exposure to oxygen with return to air for shorter periods was successfully used to acclimatize rats (117), cats (236), and guinea pigs (145) to higher oxygen tensions. Since recent investigation showed that rats can acquire a measure of adaptation to oxygen within 3 days (117), evidence is accumulating which indicates that this short-term acclimatization to oxygen is not related to the development of structural changes in the lung tissue.

It should be noted that CNS depressant drugs, such as chloroform (43), and amytal and pentobarbital (195), give some protection against the onset of oxygen-induced convulsions. Furthermore, intraperitoneal injection of tris buffer (THAM) and sodium bicarbonate were shown to be effective in delaying the appearance of convulsions (20, 207). The mechanism by which administration of these buffers affords protection is not known.

Therapeutic Use of Oxygen Under High Pressure

The suggestions Sir Francis Bacon made in his *Nova Atlantis*, to use health chambers with specially treated air to cure diseases, seem to have been realized in the recent introduction of therapy with oxygen at high pressures. High-pressure operating rooms have been developed and used for open-heart operations and other surgery. By flooding the tissues with oxygen and greatly increasing the partial pressure of oxygen in the blood plasma, organs such as the heart can be kept in functional condition even if the hemoglobin level is greatly reduced. Oxygen therapy at high pressure has also been successfully used in acute anaerobic infections and in combination with radiation therapy in the treatment of cancer. Therapeutic administration of 100 per cent oxygen at 3 atm has been extended to 2 hours, being well within the 3-hour tolerance limits established by Behnke (32) for this condition. It is to be hoped that this rapidly expanding field of high-pressure oxygen therapy will give a new impetus for further research on the causes of oxygen toxicity and on oxygen tolerance limits.

NITROGEN NARCOSIS

Exposure to air pressure equivalent to 300 feet of water produces certain changes in personality and performance which have been referred to as narcotic effects (72, 124, 196). The subjective symptoms and mental reactions consist of euphoria, overconfidence accompanied by dulling of mental ability, and difficulty of assimilating facts and making quick and accurate decisions, i.e., a general slowing of cerebration. Behnke *et al.* (37) ascribed the narcosis to nitrogen in accord with the Meyer-Overton hypothesis. It was pointed out that the symptoms are similar to those occurring in alcohol intoxication and anoxia. Quantitative tests (e.g., visual motor reaction time, arithmetic tests) under conditions of 0 to 1 atm of pressure supported the validity of the subjective symptoms reported under high pressure (231). The narcotic effects of exposure to high-pressure air are not eliminated if the oxygen tension is reduced to normal levels, but are greatly minimized when helium-oxygen mixtures are inhaled (39, 61, 92). These results were interpreted to mean that nitrogen is responsible for the narcosis induced by high-pressure air, a conclusion supported by subsequent reports dealing with hydrogen-oxygen administration during deep-sea diving (47, 256). More recent experiences with scuba diving have led to a greater emphasis on nitrogen narcosis which Cousteau (67) called "rapture of the depths." Bean (18) on the other hand has contended that carbon dioxide retention is probably the "prime etiological agent not only of compressed air intoxication but also of argon and helium narcosis." His conclusion was based, among other things, upon the finding of acute increases in alveolar CO_2 in dogs during rapid compression (19). This theory was recently supported by Seusing & Drube (227) who observed a significant increase in alveolar CO_2 tension in both air and helium dives in a dry chamber.

Based on theoretical calculations Bühlmann (56) claimed that the breathing resistance encountered during dives to great depth produces a marked CO_2 retention which he considered the sole cause of nitrogen narcosis, discounting any specific narcotic effect of nitrogen. There is ample experimental evidence showing that the work of breathing is increased under high pressure (170, 173, 174). Total pulmonary resistance was reported to be doubled at 4 atm of pressure, as compared with its sea-level value (173, 174). Maximum breathing capacity measured at various depths was found to be decreased (180, 227). Increased work of breathing and elevation of P_{O_2}, resulting in a reduction of ventilation, were implicated in the CO_2 retention found in working dives down to 99 feet when breathing nitrogen-oxygen mixtures (154). However, no relation of CO_2 retention to nitrogen narcosis was established (155). Rashbass (200) discounted CO_2 as a significant contributing factor to nitrogen narcosis. He found that men subjected to 250 feet of pressure did not show an alleviation of narcosis after the alveolar CO_2 tensions were reduced to normal levels by hyperventilation. Lanphier & Morin (157) did not find any evidence that increased gas density impairs CO_2 removal from the alveoli under conditions of constant ventilation.

Electroencephalographic recordings of human subjects exposed to a pressure of 10 atm abs showed a decrease in amplitude and increase in frequency (42, 205) which is similar to the effects of increased carbon dioxide on the EEG (217). Blocking of the EEG alpha rhythm while solving mathematical problems was found to be abolished at increased pressures, but reappeared after breathing helium-oxygen mixtures. This effect of helium cannot be considered as proof that nitrogen is the agent solely responsible for the narcosis since substitution of helium simultaneously changes the respiratory mechanics and reduces carbon dioxide retention at higher pressures (155).

Evidence so far available seems to indicate that carbon dioxide retention may enhance the development of high-pressure narcosis. However, there is no justification for excluding the narcotic action of nitrogen. Comparison of the effects of increased carbon dioxide concentrations on consciousness [recently reviewed by Schaefer (217)] with the symptomatology of pressure narcosis reveals some distinct differences. Although euphoria and overconfidence effects are similar in both conditions, there are no reports that CO_2 inhalation produces that "harsh, metallic and indefinable" taste experienced under high-pressure air (61). There is also no evidence that dissociation of depressive effects on the CNS and stimulating effects on the autonomic nervous system, characteristic of CO_2 intoxication, exists under nitrogen narcosis. Moreover, recent development of a new theory of anesthesia (192) which takes into account the interaction of inert gases with proteins offers a better understanding of the narcotic action of nitrogen. Featherstone *et al.* (93) reported a demonstrable interaction of "inert" anesthetic gases with proteins in aqueous solutions. It seems that these findings support the earlier notion of Case & Haldane (61) who stated that the narcotizing action of nitrogen cannot be adequately explained on the basis of its chemical properties and its lipoid solubility, but suggested participation of intra- and extracellular absorption processes. The same authors (61) reported some degree of habituation. The first experiences are much more alarming than later ones. Most divers seem to agree. However, there is no experimental evidence demonstrating adaptation to nitrogen narcosis.

Exposure to Synthetic Atmospheres at Normal and Increased Pressures

Recent developments in space medicine and in underwater physiological research have raised the question whether man can live in synthetic atmospheres in which nitrogen is replaced by helium and oxygen is kept at a normal level. Very few experiments have been done in this field. Mice were reported to survive exposure to 79 per cent helium and 21 per cent oxygen at 1 atm pressure for 10 weeks without harmful effects (12). It was also found that mice can tolerate 51 days of exposure to a nitrogen-free atmosphere of oxygen at a total pressure of 197 mm Hg (166). This level provided a normal inspired-O_2 tension of 150 mm Hg BTPS (body temperature, ambient pressure, saturated with water.) Several litters were born under these conditions. However, there was evidence of a critical period during the first 48 hours of exposure during which a number of animals died. The authors suggested that pulmonary atelectasis was responsible for these early deaths since the rate of collapse following obstruction of alveoli is greatly increased in the absence of an inert gas (70).

In recent experiments (1961), rats, guinea pigs, and squirrel monkeys were exposed for 14 days to a nitrogen-free atmosphere (97 per cent helium and 3 per cent oxygen) at a pressure of 7 atm (corresponding to a depth of 200 feet of sea water) and they survived

without evidence of significant physiological or histopathological changes (252). The partial pressure of oxygen was kept at 160 ± 10 mm Hg. During the 14-day exposure period rats lost on the average 46 g weight but regained 63 g during 13 weeks of recovery following exposure. The blood chemistry data, which were obtained after a 24-hour period of decompression subsequent to the 14-day exposure to 160 mm Hg O_2 and 5160 mm Hg helium, did not show any significant changes when compared with control animals. Human subjects were able to tolerate exposure to helium-oxygen mixtures for 12 hours at pressures of 2 to 2.6 atm without ill effects (89).

AIR EMBOLISM

Air embolism and interstitial emphysema are recognized hazards of decompression from high pressure and have occurred in diving and submarine escape training (165, 193), as the result of scuba diving (57), and in connection with explosive decompression at high altitudes (247). The term "air embolism" is limited to the phenomena produced by gases entering the veins or arteries from adjoining tissues. It is to be distinguished from decompression sickness or caisson disease. In the latter, prolonged exposure to high pressure produces appreciable solution of gases in tissues and blood which, upon rapid decompression, are liberated in the form of bubbles. Intravascular bubbles may produce symptoms similar to air embolism.

When the diver ascends to the surface, air contained in his lungs and other body cavities will expand. If he uses a breathing apparatus and breathes normally during ascent, the excess of expanding lung air is discharged through the breathing apparatus. However, if he holds his breath, the gases in the lungs expand as the ambient pressure diminishes. The resulting overexpansion of lung tissue may lead to interstitial emphysema and air embolism. In spite of great precautions several fatal cases of air embolism have occurred during submarine escape training (143). Since these men had carried out a normal ascent and there was no indication that they had held their breath, the question was raised whether circulatory failure could have played a critical role in the development of air embolism under these conditions.

[It would be expected that laryngospasm would be an ever-present danger under these circumstances. ED.]

This notion was supported by experimental findings in dogs which indicated that greatly increased intrathoracic pressure resulted in a systemic hypotension reflecting a decreased circulating blood volume due to pooling in the abdominal viscera (45, 48). Similar findings of systemic hypotension and abolition of arterial pulses indicating cessation of blood flow have been observed by Chillingworth & Hopkins (63) under conditions of increased pulmonary pressure. In studies of explosive decompression, reflex effects of cardiac slowing and hypotension were noted by Whitehorn *et al.* (251). More recently systematic studies were carried out on circulatory effects in the mechanism of air embolism (221). Unanesthetized dogs were compressed to 100 or 200 feet of depth and then rapidly decompressed with the trachea closed. Peak vascular, intratracheal, and intrapleural pressures recorded under these conditions are listed in table 1. The peak intratracheal pressure of the animals which developed air embolism (Group A) was 88.6 mm Hg which corresponds with the critical value of 80 mm Hg established by Polak & Adams (197). In Group B (no air embolism) this critical value was not reached, whereas animals protected with thoraco-abdominal binders (Group D) did show an elevation to 82.1 mm Hg. In the latter case the intratracheal pressure cannot be related to the degree of distention of the lungs since simultaneously the intrapleural pressure is greatly increased.

In comparing the intravascular pressures of Groups A and B, it can be noted that in the former pulmonary arterial and left atrium pressures rose to markedly higher values whereas systemic arterial pressure fell to lower levels. This indicates that the greater distention of the lungs in the animals developing air embolism results in a greater resistance in the pulmonary circulation and, consequently, in a larger fall in the systemic arterial pressure.

Of particular interest is the difference between the intratracheal and intrapleural pressure which has been called the transpulmonary, transthoracic, or transmural pressure (45, 48). It gives a quantitative estimate of the force distending the lungs and allows the establishment of a critical value at which trauma from overexpansion of the lungs occurs resulting in air embolism. Furthermore, the gradient between intratracheal and intra-atrial pressure, termed "transatrial" pressure, may be of significance since it represents the pressure gradient between the alveoli and the pulmonary venules and left heart and, therefore, the force which at sufficient magnitude produces traumatic openings of the pulmonary vessels and fascial planes of connective tissues leading to penetration of intra-alveolar gases into the pul-

TABLE 1. *Control and Peak Pressures in Dogs During "Ascents" from 100 or 200 Feet Equivalent Depth with Trachea Closed*

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

Group A, animals without binders which developed air embolism; B, animals without binders which did not develop air embolism; C, animals with abdominal binders (both developed air embolism); and D, animals with thoracoabdominal binders (neither developed air embolism). N, number of animals. As, number of ascents. Figures represent pressures in mm Hg, with their standard deviations, based on means weighted by the number of ascents for N animals. [From Schaefer *et al.* (221).]

TABLE 2. *Effects of Decompression from Depth with Trachea Closed: Maximum Gradients Attained*

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

I.T., intratracheal; I.P., intrapleural; L.A., left atrial; and P.A., pulmonary arterial. The difference between transpulmonary pressures for Groups A and B is statistically significant ($P < 0.01$ when determined by means of Fisher's "t" factor); the same is true for the difference between transatrial pressures. N (number of animals) and As (number of ascents) are not the same as in table 1 since a complete set of data could not be obtained in all animals. [From Schaefer *et al.* (221).]

monary circulation. Transpulmonary, transatrial and transcapillary pressures are listed in table 2. When all the animals that developed air embolism (Groups A and C) are compared with those that did not (Groups B and D), the critical levels of transpulmonary and transatrial pressure gradients become apparent. When the transpulmonary gradient is in excess of 60 to 70 mm Hg, or the transatrial in excess of 55 to 65 mm Hg, air embolism does occur. Under these conditions, the transcapillary pressure (difference between pulmonary artery and left atrium pressure) has reached 20 to 30 mm Hg.

In experiments with dogs wearing thoracoabdominal binders, it was shown that high intratracheal pressures of 180 to 200 mm Hg can safely be withstood. Under these conditions, increases in intrapleural pressure parallel those of the intratracheal pressure and consequently the transpulmonary pressure does not exceed the critical level of approximately 60 mm Hg (221). It is for the same reason that the pressures during coughing and the Valsalva experiment—which are much greater than the intratracheal pressures mentioned in the tables (see Chapter 52 by Sharpey-Schafer in this volume)—do not result in interstitial emphysema or air embolism.

The circulatory events leading to air embolism in a dog decompressed from 200 feet are illustrated in figure 4. At a depth corresponding to approximately 30 feet, the pressures in the pulmonary artery and the venous pressure reached a peak which was preceded by two dips reflecting respiratory efforts. It is noteworthy that at this point all circulatory pressures appeared to have approximately the same value of 50 mm Hg, and that cardiac action had practically

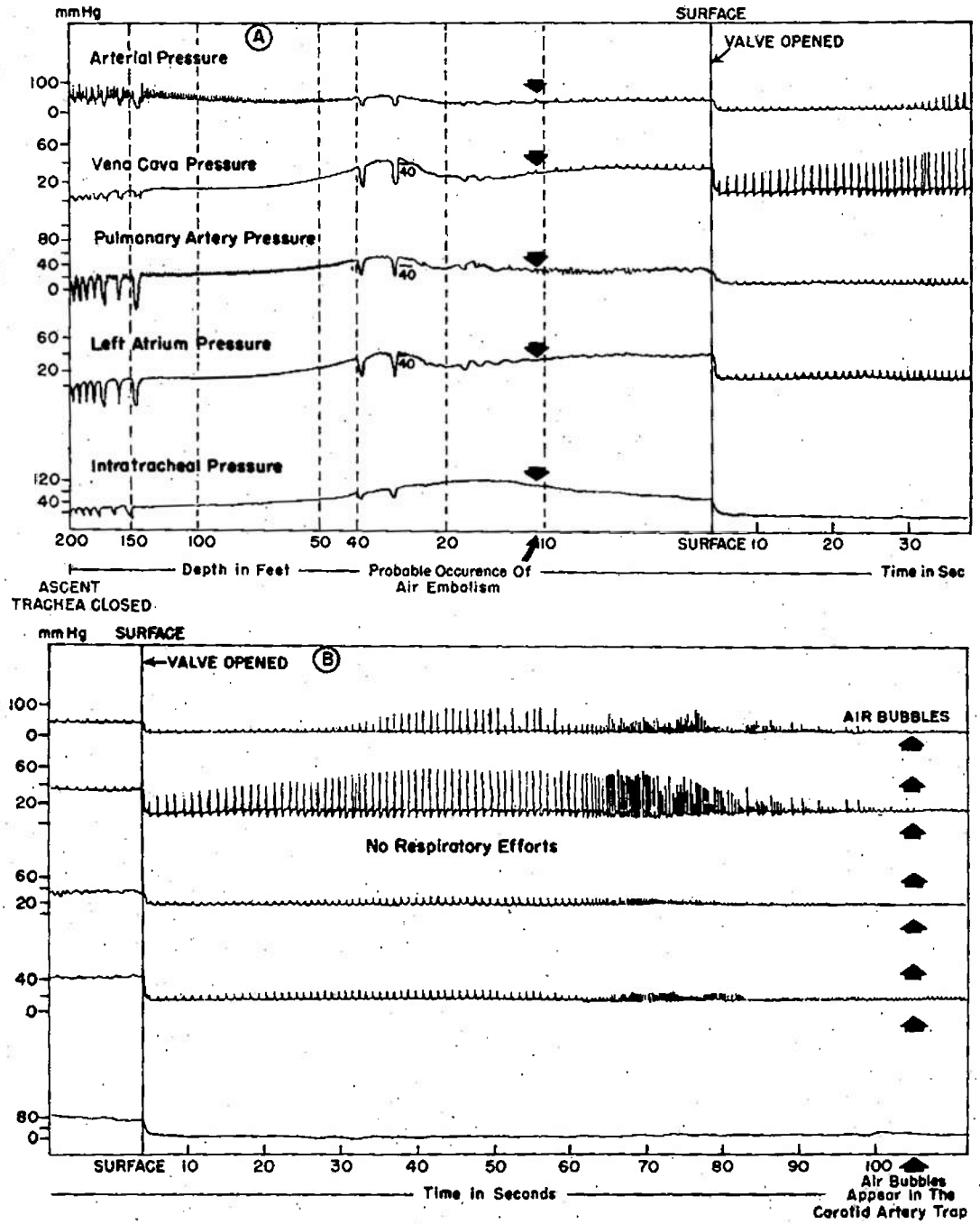

FIG. 4. Experiment 23 showing development of fatal air embolism. Intracavity and intravascular pressures in dogs decompressed from 200-foot equivalent depth who died of air embolism. Record 4*A* continuous with 4*B*. [From Schaefer *et al.* (221).]

stopped and pulses were eliminated from the records. At approximately 10 feet of depth, pulses reappeared in the record of the circulatory pressures simultaneously with a drop in the intratracheal pressure. This would appear to be the moment at which air embolism occurred. After reaching the surface and opening the valve, the vena caval pulse pressure immediately reached about 40 mm Hg, compared

with 5 mm Hg at the beginning of the ascent. There was a high pulse pressure in the vena cava suggesting tricuspid insufficiency associated with distention of the right heart. Venous return was probably also augmented. The pulmonary artery and left atrial pulse pressures rose, but somewhat later and to a much lesser degree than in the case of the vena cava. These pressures never reached the initial values recorded prior to ascent. The records show, quite a few seconds later, signs of a failing heart. The chamber was entered 120 sec after it reached surface values; bubbles were observed in the carotid artery trap, whereas the trap for the jugular vein did not show any bubbles.

Intracavitary and intravascular pressures recorded in dogs decompressed from 200 feet equivalent depth who survived the ascent showed similar changes, only less pronounced, than those shown in figure 4. The transitory circulatory failure observed under both conditions cannot be considered therefore to contribute directly to the development of air embolism. The period of arterial hypotension, lasting for 20 min or less, will not in itself be fatal or produce permanent harm.

After release of the tracheal obstruction, the systemic arterial pressure is promptly restored in animals which are able to recover. One of the beneficial effects of thoracoabdominal binders is the maintenance of the aortic pressure with little fall throughout the ascent.

Under the experimental conditions described, there was sufficient evidence to suggest that air embolism developed by way of the pulmonary veins. In all experiments resulting in air embolism, gas was found in the bubble traps placed in the carotid arteries, while the bubble traps in the jugular veins frequently remained empty.

It has been mentioned that in two instances of fatal air embolism which occurred during submarine escape training, apparently normal ascents had been carried out (143). This has suggested the possibility of involuntary air trapping in the lungs. Subsequently, two other cases of air embolism were reported with concrete evidence of local air trapping (163). In the one fatal case, a broncholith of tuberculous origin acted as a ball valve within a subsegmental bronchus. In the other patient, who survived, the mechanism of the bronchial obstruction was not apparent, but a large bulla was demonstrated roentgenographically after decompression. This was almost entirely absorbed within 36 hours of the patient's return to atmospheric pressure (163). Pulmonary function studies carried out on this patient after his recovery did not reveal any measurable volume of "trapped gas" in the lungs.

DECOMPRESSION SICKNESS

Divers and caisson workers who have been exposed to increased pressures are liable on their return to atmospheric pressure to develop a variety of symptoms generally known as decompression sickness. Similar conditions exist for the aviator upon rapid decompression from normal atmospheric pressure to altitude. Incidence of more severe symptoms of decompression sickness has been reported to be about 5 per cent in deep-sea diving and 2 per cent in caisson work (29).

Manifestations of decompression sickness include numbness, weakness and pains (bends) in the extremities, cardiopulmonary symptoms (chokes), paralysis, and chronic bone lesions. Bends, the most common symptom of decompression sickness, is characterized by throbbing pains felt frequently in joints, deep muscles, and bones. The onset of pain may be preceded by a feeling of numbness and weakness. Chills, fever, and sweating may be associated with bends. The onset of symptoms varies greatly and may occur within 1 to 18 hours after decompression (162).

Chokes, which are less frequent than bends, are symptoms of pulmonary distress. The first manifestations are usually substernal pain during deep inspiration. Then breathing becomes shallow and rapid, the skin becomes cyanotic and gray, and the pulse rate falls indicating impending collapse. Severe attacks of coughing may precede loss of consciousness. These symptoms develop somewhat more slowly than bends.

Etiology of Decompression Sickness

It was demonstrated experimentally by Bert (43) that gas, chiefly nitrogen, which goes into solution in the blood and tissues during exposure to compressed air is liberated in the form of bubbles during rapid decompression. He concluded that decompression sickness is caused by interference of gas bubbles with the circulation in the central nervous system and in other tissues. He also noted that slow decompression prevented bubble formation and the resulting decompression sickness, and recommended the use of oxygen breathing by divers and caisson workers to hasten nitrogen elimination. These observations were subsequently confirmed and extended (116, 123). Direct

observations of gas bubbles in pial vessels of cats following rapid decompression were made by Wagner (249). Because of the great variety of clinical symptoms of decompression sickness, it was postulated that its etiology is not limited to gas bubbles but that other humoral agents and reflexes might play a role (171).

Reviewing the pathogenesis of decompression sickness, Catchpole & Gersh (62) concluded that intravascular gas bubbles are the primary pathogenic agent which can account for most of the important aspects of decompression sickness. Furthermore, it was noted that extravascular bubbles occur in severe cases of decompression from high-pressure atmospheres but are restricted to lipoid-rich structures.

Comparing necropsy findings in airmen with those of caisson workers and divers, Haymaker & Johnston (115) found that the lesions in the spinal cord were basically the same, although much more severe after decompression from high pressure. This difference was thought to be related to a larger amount of circulating nitrogen bubbles under the latter conditions. Behnke (29) calculated the quantity of gas which has to be released from the tissues of a 70 kg man after decompression for 30 min from 5 to 1 atm and from 1 to 0.2 atm. The total gas volume is 2880 ml. However, the nitrogen released by the diver is 2 liters, while that of the airmen decompressed to altitude is about 1 liter. Furthermore, Haymaker & Johnston (115) observed fat emboli in cases where traumatic air embolism could be ruled out as a causative factor. The authors concluded that fat emboli, together with other cellular degradation products such as lipases, histamine-like substances and proteolytic enzymes, might have reached the blood stream and, acting on vessel walls, probably caused pooling of blood resulting in circulatory collapse. This hypothesis corresponds to a certain degree with the view held by Masland (171), Ferris *et al.* (95), and Gerbis & Koenig (99) who suggested that the grave states of shock after decompression are caused by the products of widespread tissue damage rather than by nitrogen bubble embolization. On the other hand, Behnke (28, 29) maintains that circulatory collapse in decompression sickness is produced by intravascular nitrogen bubbles. He cites evidence (35) from experiments in which dogs were rapidly decompressed after exposure to 5 atm of pressure for 1½ hours which incriminates intravascular bubbles as the cause of tachypnea and limitation of deep inspiration. Tachypnea, slow pulse rate, and fall in blood pressure, characteristic of severe decompression sickness in dogs, indicate impending collapse or irreversible shock. However, with information accumulating as it has in recent years, it becomes more apparent that intravascular bubble formation is influenced by a number of endogenous factors. Medication with diuretics and electrolyte treatment resulting in increased blood viscosity (254) seem to reduce development of intravascular bubbles. One excellent, more recent review of the pathogenesis of decompression sickness was given by Haymaker (114).

Bubble Formation

The physical conditions which must be present in liquid or tissues for the formation of gas bubbles have been studied extensively by Harvey (111). The tissues must contain permanent gas nuclei which, according to Harvey, are defined as "any small invisible mass of gas, usually but not always attached to a surface." Gas nuclei may arise from previous contact of a surface with a gas phase. They are not normally present in blood or tissues, as shown in animal experiments (112). However, gas nuclei can be generated if sufficient force is applied to open up small cavities in a fluid. The pressure difference (P) between the total gas tension in the liquid (t) and the hydrostatic pressure in the liquid (p) has to be of the order of 100 to 1000 atm.

$$P = t - p \qquad (1)$$

Such pressure differences may occur in submicroscopic areas subjected to supersaturation at high pressures followed by rapid decompression. The cavities in the liquid contain water vapor and are rapidly filled by gas molecules which move in from the surface of the cavity in proportions depending on the solubility of the gases rather than on their partial pressures (111). In the presence of gas nuclei, bubbles may be formed either by a decrease in hydrostatic pressures (p) or an increase of gas tension (t) since both tend to increase P. Although it is very difficult to produce cavities or bubbles in liquid under static conditions, whether great negative pressures are applied or high supersaturation of gases is obtained, motion of liquid will greatly facilitate bubble formation.

In the circulation, local decreases in p are most likely to occur since the liquid can be pulled away from the surface easily, leaving a cavity behind. Furthermore, local vasoconstriction, turbulence, and local tissue pulling resulting from muscular exercise favor bubble formation. If a blood vessel is constricted, the blood flow will be decreased and the

hydrostatic pressure will fall at the constriction in accordance with Bernoulli's law. Since the flow rate has to be rather fast and the constriction sufficiently great to produce the extremely low pressures necessary for breaking up the fluid into cavities (Reynolds' cavitation), it is problematic whether these conditions are attained in the body. However, this phenomenon may result from mechanical tensions produced during physical exercise prior to decompression. In any case, the lowered hydrostatic pressures caused by local vasospasm and muscular exercise favor bubble formation. Similar decreases in pressures will occur in vortices of turbulent flow which are found in the heart (111).

Manipulation of excised tissues, e.g., cutting and pulling, will result in bubble formation during decompression (112). It has been suggested that stretching of tissues produces high enough tensions on their liquid contents to cause a tearing of the liquids and subsequent cavity and bubble formation. Connective tissues contain the most extensive bubbles of all manipulated tissues in decompression, and it is probably significant that bends are located predominantly in regions of connective tissue.

Theoretical Relation of Symptoms to Bubble Size

Once a bubble has formed during decompression, the production of symptoms will depend on several factors as analyzed by Nims (184). Briefly, he expresses these factors in the equation

$$P_{N_2} + P_{CO_2} + P_{O_2} + P_{H_2O} - H = D + \left(\frac{2X}{r}\right) \qquad (2)$$

where P_{N_2}, P_{CO_2}, P_{O_2} and P_{H_2O} refer to the partial pressures of the indicated gases in the bubble, H is that proportion of the hydrostatic pressure of the fluid surrounding the bubble which is independent of the volume of the bubble, D is that fraction of the hydrostatic pressure which is a function of the volume of the bubble and therefore may be referred to as the deformation pressure, X is the gas-water interfacial tension of the fluid, and r is the radius of the bubble. When the deformation pressure D reaches a threshold value, nerve fibers are stimulated and symptoms will occur. If D continues to increase, tearing of tissue membranes will take place.

Equation (2) contains a few obvious features which are consistent with observations of decompression sickness. Thus, D may be decreased either by the decrease of partial pressure of one or more of the gases in the bubble or by an increase in H, the non-bubble-dependent hydrostatic pressure. With regard to the former, denitrogenation not only decreases the amount of nitrogen in the body but also decreases the P_{N_2} of any bubbles formed during decompression. Since, of the four gases, nitrogen is normally present in the largest amounts in decompression bubbles, this becomes a significant method of reducing D. It should be noted, however, that CO_2 is also present in large amounts and is a highly soluble and rapidly diffusing gas. Thus any factor tending to increase CO_2 production or stores, such as exercise, will tend to increase P_{CO_2}. On the other hand, the normally low tissue oxygen tension and relatively constant water vapor pressure reduce P_{O_2} and P_{H_2O} to essential constants in this equation. However, decompression sickness can also occur as a result of supersaturation of tissues with oxygen. A subject exposed to oxygen at 2 to 3 atm developed bends on decompression to atmospheric pressure (184). Rashbass (199), who saw a similar case, carried out experimental studies to determine whether oxygen contributes to decompression sickness (201). Rats exposed to different nitrogen-oxygen mixtures at pressures from 90 to 160 psi were decompressed rapidly and the LD_{50} determined. It was concluded that oxygen had a small but significant effect on the occurrence of decompression sickness.

Donald (82) demonstrated severe but very transient oxygen bends in goats decompressed after 60 min exposure to 36 per cent N_2 and 64 per cent O_2 at 5.54 atm. If the animals were subjected separately to the same O_2 supersaturation and N_2 supersaturation which, combined, resulted in decompression sickness, no symptoms were produced. It was assumed that oxygen would enter "silent nitrogen bubbles" because of its greater solubility and diffusion, thus precipitating bends. These findings are compatible with equation (2) since an increase in P_{O_2} increases D.

Aside from the gas tension effect predicted by equation (2), it is also seen that any increase in hydrostatic pressure (H) will tend to protect against the occurrence of symptoms. The most obvious example of this is the effectiveness of recompression in obliterating these symptoms. Moreover, since symptoms are localized, it may be assumed that their locality is dependent upon the local hydrostatic pressure. This would account for the effectiveness of direct application of local pressure to the part affected (7).

Nims' mathematical analysis of environmental factors affecting susceptibility to bends also provides

a contribution to the controversial question whether intravascular or extravascular bubbles produce bends. It is very difficult to decide this in X-ray pictures of the joints of subjects having bends. On the other hand, the behavior of bends under various experimental conditions seems to support the extravascular theory. Once pain has appeared, recompression will relieve the pain. On reascent, pain will reappear at the same site. Rodbard (204) was able to demonstrate this immediate recurrence of pain on the same site for periods up to 4 hours. These findings cannot be explained on the basis of the intravascular bubble theory.

Using equation (2) it is easy to understand that an increase in hydrostatic pressure (on recompression) will reduce D below the threshold value. The bubble could still be present as a "silent" bubble which does not produce symptoms. On reascent, pain reappears on the same sites because D has become larger than the threshold value.

Protection from Decompression Sickness

Since, as described above, the primary factor involved in the production of decompression sickness is the supersaturation of the body fluids with gas, protection of the diver is accomplished by attempting to minimize this phenomenon. This may be undertaken by decompressing in stages, allowing time for sufficient nitrogen washout at each stage. Also, oxygen may be breathed during part of the decompression period in order to hasten nitrogen elimination. Lastly, another gas such as helium may replace nitrogen in the breathing mixture during the period of high pressure, thus favorably altering some of the washout characteristics of the dissolved gas as well as reducing the danger of high inert-gas pressure narcosis.

The minimization of supersaturation by means of slow or stepwise decompression, as a physiological procedure, is based primarily upon the observations of Boycott *et al.* (52). Provided compression is limited to 2 atm, return to 1 atm can be made as rapidly as desired without danger of bends. Moreover, this fact was found to be independent of the length of time of exposure to high pressure. Generalizing from this observation, it was concluded that if the P_{N_2} in the body is not greater than twice the total amount of ambient pressure, bubbles will not form. On this basis, decompression tables were prepared, theoretically permitting a diver to ascend from depth in steps, stopping long enough at each step to allow sufficient nitrogen washout to occur before proceeding to the next step, thus avoiding decompression symptoms. Extensive experience with this type of decompression has led to the development of semiempirical tables allowing for somewhat more rapid decompression. However, decompression symptoms may still occur on occasion and are usually treated by immediate recompression in a chamber, followed by a very conservative schedule of return to 1 atm.

The primary drawback of the decompression table based on the Haldane principle is the length of time it takes to surface a diver after a deep dive. Decompression time has been shortened 30 to 50 per cent by breathing 100 per cent oxygen during the latter stages of decompression, which facilitates more rapid elimination of nitrogen. This has been accomplished technically in surface decompression (245) utilizing a pressure chamber and also in the Davis submersible chamber technique (75).

A re-examination of Haldane's method of decompression began when it was discovered that the 2 to 1 decompression ratio of the tissue partial pressure was dangerous under conditions of prolonged dives to depths of 120 to 200 feet of sea water. Haldane's concept of nitrogen elimination is based on the assumption that each tissue can be assigned a half saturation time varying from 5 to 75 min and that the tissues will saturate and desaturate exponentially with time. Shaw *et al.* (228) were able to demonstrate in dog experiments that nitrogen saturation and desaturation proceeds at approximately equal rates. The semilogarithmic nitrogen elimination curves which were obtained could be broken down into five or more components representing fast and slow tissues (34). On the basis of nitrogen elimination studies during oxygen breathing, Jones (137) proposed that bends are produced by bubble formation in muscles while Lundin (164) maintained that nitrogen bubbles are formed in fat tissues. However, analysis of 2,000 dives to depths between 100 and 200 feet demonstrated that the various tissues of the body will tolerate decompression ratios varying from 5 to 1 for rapidly saturating (5 min) tissue down to 1.8 to 1 for the slowly saturating (75 min) tissues (113). This could not have been predicted on the basis of Haldane's theory. As a result, diving decompression tables were modified to avoid unnecessary deep decompression stops involving fast tissue clearance and to use lower surfacing ratios than were previously considered safe (90, 245). Minimal decompression curves (depth-time combinations from which a diver can surface without decompression

stops) for diving with helium-oxygen mixtures were determined by Duffner (88).

In addition to the empirical modification of the original Haldane decompression tables, the basic concept of Haldane has been questioned by Hempleman (118). He pointed out that the postulate of equal saturation and desaturation times of tissues with inert gases like nitrogen can hold only when two well-stirred solutions are present on either side of a permeable membrane. This condition is realized in the blood but not in the tissues. It was also assumed that a single "tight" tissue, as proposed by Nims (184), would be the controlling factor in the development of bends. Based on this approach, and in the hope of making practicable repeat dives on a single day, new tables were calculated which did not prove to be as satisfactory as those developed on Rashbass's concept of pressure excess (199). Further modification was introduced by Crocker (69) who used a bubble regression curve covering the relationship among tissue saturation, bubble size, and bubble pressure for calculations of tables which were successfully tested in sea trials.

In recent experimental studies with goats, additional evidence was produced indicating unequal rates of uptake and elimination of nitrogen in tissues during diving (119). Hempleman established first a relationship between time and depth, and risk of bends in single nonstop dives and demonstrated that this relationship cannot be used for double dives which implies that a discontinuity in rate of gas exchange developed in the double-dive experiment.

The world's record dive in the open sea was accomplished in 1956 by a diver of the Royal Navy who reached 600 feet using a helium-oxygen mixture. Dives to greater depth have recently been carried out by H. Keller (Switzerland) who reached 820 feet in a wet chamber of the French Navy in Toulon and 720 feet (220 m) in Lake Maggiore, Switzerland. He did not have any signs of decompression sickness after ascent. Prior to his dives he breathed oxygen for periods of 2 hours and 1 hour, respectively, thereby eliminating most of the nitrogen from the body. He also used oxygen decompression, although the exact composition of the breathing mixtures used during the dive and ascent was not revealed (141).

Adaptive Changes Related to Decompression Sickness

Susceptibility to decompression sickness is known to vary widely among different subjects and even in individuals from day to day. In spite of great analytical efforts, no satisfactory explanation has been offered so far. It would seem therefore doubtful whether any adaptive changes influencing resistance to decompression sickness could manifest themselves under these circumstances.

In regard to aviator's decompression sickness, Balke (10) noted that incidence and intensity of bends during decompression tests to 38,000 feet altitude are markedly reduced following altitude acclimatization for several weeks at 14,160 feet (Mt. Evans).

In decompression experiments with rats, reduction in the development of intravascular bubble formation was observed following acclimatization to 3,000 to 4,000 m (9,800 to 13,200 feet) for 35 to 40 hours which appeared to be related to the decreased amount of nitrogen present in the body after acclimatization to altitude (253).

The older literature on caisson work contains references to practical experiences indicating that some kind of acclimatization to decompression sickness following exposure to higher pressures might exist. It remained for Paton & Walder (191) to establish this acclimatization beyond doubt in a careful analysis at the Tyne Tunnel project.

Taking into account the "natural selection" of susceptible individuals and the random variation among them, a significant decline of the bends rate was found during the first 2 weeks of caisson work which could only be explained by acclimatization. Another study (108) carried out more recently during the construction of a tunnel under the Thames at Dartford (in which Paton and Walder participated) confirmed previous findings on acclimatization and also showed that increased resistance to bends was slowly lost when the subjects stayed away from work for longer periods of time.

No convincing theory explaining acclimatization to decompression sickness has been advanced because of our lack of knowledge in this field.

REFERENCES

1. ALELLA, A., AND E. MEDA. Frequenza cardiaca durante la respirazione di O_2 nell'uomo ed importanza del vago. *Boll. Soc. Ital. Biol. Sper.* 24: 581, 1948.

2. ALVIS, H. J. Breathholding breakpoint at various increased pressures. *U. S. Naval Med. Res. Lab. Rept.* No. 177, 1951.

3. ANDERSON, H. T. Depression of metabolism in the duck during diving. *Acta Physiol. Scand.* 46: 234, 1959.
4. ANDERSON, H. T. Physiological adjustments to prolonged diving in the American alligator. *Acta Physiol. Scand.* 53: 23, 1961.
5. ANTHONY, A. J. Sauerstoffatmung, Blut und Kreislauf. *Luftfahrtmed.* 4: 11, 1940.
6. ANTHONY, A. J., AND H. KUEMMEL. Herzfrequenz und Herzstromkurve bei Gesunden nach kurzdauernder Sauerstoffatmung. *Z. Ges. Exptl. Med.* 106: 303, 1939.
7. ANTHONY, R. A., R. W. CLARKE, A. LIBERMAN, L. F. NIMS, J. TEPPERMAN, AND S. M. WESLEY. Effects of local compression, impairment of venous return and arterial tourniquet upon the intensity of established "bends" pain. *Natl. Acad. Sci.–Natl. Res. Council Comm. Aviation Med. Rept.* No. 143, 16 June, 1943.
8. ASMUSSEN, E., AND M. NIELSEN. Studies in the regulation of respiration in heavy work. *Acta Physiol. Scand.* 12: 121, 1947.
9. BAKER, S. P., AND F. A. HITCHCOCK. Immediate effects of inhalation of 100% oxygen at one atmosphere on ventilation volume, carbon dioxide output, oxygen consumption and respiratory rate in man. *J. Appl. Physiol.* 10: 363–366, 1957.
10. BALKE, B. Parameters of human adaptation to altitude. In: *Physics and Medicine of the Atmosphere and Space*, edited by O. O. Benson and H. Strughold. New York: Wiley, 1960.
11. BARACH, A. L. The effects of atmospheres rich in oxygen on normal rabbits and on rabbits with pulmonary tuberculosis. *Am. Rev. Tuberc.* 13: 293, 1926.
12. BARACH, A. L. Use of helium as a new therapeutic gas. *Proc. Soc. Exptl. Biol. Med.* 32: 462–464, 1934.
13. BARACH, A. L., M. ECKMAN, E. T. OPPENHEIMER, C. RUMSEY, JR., AND M. SOROKA. Observations on methods of increasing resistance to oxygen poisoning and studies of accompanying physiological effects. *Am. J. Physiol.* 142: 462–475, 1944.
14. BARACH, A. L., AND A. STEINER. Effect of inhalation of high oxygen concentrations, with and without carbon dioxide, on the electrocardiogram. *Proc. Soc. Exptl. Biol. Med.* 45: 175–179, 1940.
15. BARLOW, H. B., AND F. C. MACINTOSH. Shallow water blackout. Royal Naval Physiol. Lab. Rept. R.N.P. 44/125, U.P.S. 48(a), 1944.
16. BATEMAN, J. B. Preoxygenation and nitrogen elimination. Pt. I. Review of data on value of preoxygenation in prevention of decompression sickness. In: *Decompression Sickness*, edited by J. F. Fulton. Philadelphia: Saunders, 1951, chap. IX, pp. 242–277.
17. BAZETT, H. C., S. THURLOW, C. CROWELL, AND W. STEWART. Studies on the effect of baths on man. II. The diuresis caused by warm baths, together with some observations on urinary tides. *Am. J. Physiol.* 70: 430–452, 1924.
18. BEAN, J. W. Effects of oxygen at increased pressure. *Physiol. Rev.* 25: 1–147, 1945.
19. BEAN, J. W. Tensional changes of alveolar gas in reactions to rapid compression and decompression and question of nitrogen narcosis. *Am. J. Physiol.* 161: 417–425, 1950.
20. BEAN, J. W. Tris buffer, CO_2 and sympathico-adrenal system in reactions to O_2 at high pressure. *Am. J. Physiol.* 201: 737–739, 1961.
21. BEAN, J. W. Cerebral O_2 in exposure to O_2 at atmospheric and higher pressures and influence of CO_2. *Am. J. Physiol.* 201: 1192–1198, 1961.
22. BEAN, J. W., AND P. JOHNSON. The hypophysis as a determinant in the reaction of the mammal to oxygen at high pressure. *Am. J. Physiol.* 170: 508–517, 1952.
23. BEAN, J. W., AND P. C. JOHNSON. Adrenocortical response to single and repeated exposure to oxygen at high pressure. *Am. J. Physiol.* 179: 410–414, 1954.
24. BEAN, J. W., AND P. C. JOHNSON. Epinephrine and neurogenic factors in the pulmonary edema and CNS reactions induced by O_2 at high pressure. *Am. J. Physiol.* 180: 438–444, 1955.
25. BEAN, J. W., AND G. ROTTSCHAFER. Reflexogenic and central structures in oxygen poisoning. *J. Physiol., London* 94: 294–306, 1938.
26. BEAN, J. W., AND C. W. SMITH. Hypophyseal and adrenocortical factors in pulmonary damage induced by O_2 at atmospheric pressure. *Am. J. Physiol.* 172: 169–174, 1953.
27. BEHNKE, A. R. Effects of high pressures; prevention and treatment of compressed air illness. *Med. Clin. N. Am.* 26: 1213, 1942.
28. BEHNKE, A. R. Decompression sickness following exposure to high pressure. In: *Decompression Sickness*, edited by J. F. Fulton. Philadelphia: Saunders, 1951, chap. III, pp. 53–89.
29. BEHNKE, A. R. Decompression sickness. *Military Med.* 117: 247, 1955.
30. BEHNKE, A. R. Oxygen decompression. *Natl. Acad. Sci. Natl. Res. Council Publ. No.* 377, 1955, p. 61.
31. BEHNKE, A. R. Effects of oxygen and nitrogen on consciousness. In: *Environmental Effects on Consciousness*, edited by K. E. Schaefer. New York: Macmillan, 1962, p. 117.
32. BEHNKE, A. R., H. S. FORBES, AND E. P. MOTLEY. Circulatory and visual effects of oxygen at 3 atmospheres pressure. *Am. J. Physiol.* 114: 436–442, 1935–36.
33. BEHNKE, A. R., F. S. JOHNSON, J. R. POPPEN, AND E. P. MOTLEY. The effect of oxygen on man at pressures from 1 to 4 atmospheres. *Am. J. Physiol.* 110: 565–572, 1934–35.
34. BEHNKE, A. R., AND L. A. SHAW. The application of measurements of nitrogen elimination to the problem of decompressing divers. *U. S. Naval Med. Bull.* 35: 219, 1937.
35. BEHNKE, A. R., L. A. SHAW, A. C. MESSER, R. M. THOMSON, AND E. P. MOTLEY. The circulatory and respiratory disturbances of acute compressed-air illness and the administration of oxygen as a therapeutic measure. *Am. J. Physiol.* 114: 526–533, 1935–36.
36. BEHNKE, A. R., L. A. SHAW, C. W. SHILLING, R. M. THOMSON, AND A. C. MESSER. Studies on the effects of high oxygen pressure. Effect of high oxygen pressure upon the carbon-dioxide and oxygen content, the acidity and the carbon-dioxide combining power of the blood. *Am. J. Physiol.* 107: 13–28, 1934.
37. BEHNKE, A. R., R. M. THOMSON, AND E. P. MOTLEY. The psychologic effects from breathing air at 4 atmospheres pressure. *Am. J. Physiol.* 112: 554–558, 1935.
38. BEHNKE, A. R., R. M. THOMSON, AND L. A. SHAW. The rate of elimination of dissolved nitrogen in man in rela-

tion to the fat and water content of the body. *Am. J. Physiol.* 114: 137–146, 1935.
39. BEHNKE, A. R., AND O. D. YARBROUGH. Physiologic studies of helium. *U.S. Naval Med. Bull.* 36: 542, 1938.
40. BENEDICT, F. G., AND H. L. HIGGINS. Effects on men at rest of breathing oxygen-rich gas mixtures. *Am. J. Physiol.* 28: 1–28, 1911.
41. BENNETT, G. A., AND F. J. C. SMITH. Pulmonary hypertension in rats living under compressed air conditions. *J. Exptl. Med.* 59: 181, 1934.
42. BENNETT, P. B., AND A. GLASS. Electroencephalographic and other changes induced by high partial pressures of nitrogen. *Electroencephalog. Clin. Neurophysiol.* 13: 91, 1961.
43. BERT, P. *La Pression barométrique, recherches de physiologie expérimentale.* Paris: Masson, 1878, 1168 pp. (English translation: *Barometric Pressure. Researches in Experimental Physiology*, translated by M. A. Hitchcock and F. A. Hitchcock. Columbus, Ohio: College Book Co., 1943, 1055 pp.)
44. BINGER, C. A. L., J. M. FAULKNER, AND R. L. MOORE. Oxygen poisoning in mammals. *J. Exptl. Med.* 45: 849, 1927.
45. BJURSTEDT, H. Influence of the abdominal muscle tone on the circulatory response to positive pressure breathing in anesthetized dogs. *Acta Physiol. Scand.* 29: 145, 1953.
46. BJURSTEDT, H., AND C. M. HESSER. Carbon dioxide exchange during transient exposure to high atmospheric pressure under breath holding (simulated skin diving to 40 meters). *Tidskr. Milit. Halsov.* 81: 183, 1956.
47. BJURSTEDT, H., AND G. SEVERIN. The prevention of decompression sickness and nitrogen narcosis by the use of hydrogen as a substitute for nitrogen (the Arne Zetterstrom Method for Deep-sea Diving). *Military Surgeon* 103: 107, 1948.
48. BJURSTEDT, H., E. H. WOOD, AND A. ASTRAM. Cardiovascular effects of raised airway pressure. *Acta Physiol. Scand.* 29: 190, 1953.
49. BOND, G. F., AND K. E. SCHAEFER. Carbon dioxide exchange during skindiving. In: *Man's Dependence on the Earthly Atmosphere*, edited by K. E. Schaefer. New York: Macmillan, 1962, p. 335.
50. BOND, G. F., R. D. WORKMAN, AND W. F. MAZZONE. Deep submarine escape. *U.S. Naval Med. Res. Lab. Rept.* No. 346, 1960.
51. BORUM, V. F., K. E. SCHAEFER, AND B. T. HASTINGS. The effect of exposure to elevated carbon dioxide tension over a prolonged period on basal physiological functions and cardiovascular capacity. *U.S. Naval Med. Res. Lab. Rept.* No. 241, 1954.
52. BOYCOTT, A. E., G. C. C. DAMANT, AND J. S. HALDANE. The prevention of compressed air illness. *J. Hyg.* 8: 342, 1908.
53. BOYCOTT, A. E., AND C. L. OAKLEY. Oxygen poisoning in rats. *J. Pathol. Bacteriol.* 35: 468, 1932.
54. BREU, W. Elektrokardiographische Untersuchungen bei Caissonarbeitern. *Wien. Klin. Wochschr.* 53: 400, 1940.
55. BROOKS, H. A study of blood pressure in compressed air workers. *Med. Record N. Y.* 71: 855, 1907.
56. BÜHLMAN, A. A. La physiologie respiratoire au cours de la plongée sous-marine. *J. Suisse Med.* 91: 774, 1961.
57. BURNS, W. T. Medical problems of skin diving. *J. Am. Med. Assoc.* 159: 5, 1955.
58. CAMPBELL, J. A. Effect of breathing oxygen at high pressures upon tissue gas tensions. *J. Physiol., London* 68: 81, 1929–30.
59. CAREY, C. R., AND K. E. SCHAEFER. Biphasic pattern in opposite "on and off" CO_2 effects on Metrazol seizures. *Federation Proc.* 16: 19, 1957.
60. CAREY, C. R., K. E. SCHAEFER, AND H. J. ALVIS. Effect of skin diving on lung volumes. *J. Appl. Physiol.* 8: 519–523, 1955–56.
61. CASE, E. M., AND J. B. S. HALDANE. Human physiology under high pressure. I. Effects of nitrogen, carbon dioxide and cold. *J. Hyg.* 41: 225, 1941.
62. CATCHPOLE, H. R., AND L. GERSH. Pathogenetic factors and pathological consequences of decompression sickness. *Physiol. Rev.* 27: 360–397, 1947.
63. CHILLINGWORTH, F. P., AND R. HOPKINS. Physiologic changes produced by variations in lung distention. II. Efficiency of the pulmonary circulation in overcoming obstruction. *Am. J. Physiol.* 51: 289–302, 1920.
64. CLAMANN, H. G., AND H. BECKER-FREYSENG. Einwirkung des Sauerstoffs auf den Organismus bei höherem als normalem Partialdruck unter besonderer Berücksichtigung des Menschen. *Luftfahrtmed.* 3: 1, 1939.
65. CLAMANN, H. G., H. BECKER-FREYSENG, AND G. LIEBEGOTT. Das allgemeine Verhalten und die morphologischen Lungenveränderungen verschiedener Tierarten bei langer Einwirkung erhöhten Sauerstoffteildrucks. *Luftfahrtmed.* 5: 17, 1940–41.
66. COMROE, J. H., R. D. DRIPPS, P. R. DUMKE, AND M. DEMMING. Oxygen toxicity: the effect of inhalation of high concentrations of oxygen for twenty-four hours on normal men at sea level and at a simulated altitude of 18,000 feet. *J. Am. Med. Assoc.* 128: 710, 1945.
67. COUSTEAU, J. R. *The Silent World.* London: Reprint Society, 1954.
68. CRAIG, A. B., JR. Causes of loss of consciousness during underwater swimming. *J. Appl. Physiol.* 16: 583–586, 1961.
69. CROCKER, W. E. Investigation into decompression tables. Revised tables. Royal Naval Physiological Lab. Rept. 58/902, 1957.
70. DALE, W. A., AND H. RAHN. Rate of gas absorption during atelectasis. *Am. J. Physiol.* 170: 606–615, 1952.
71. DALY, W., AND J. ST. BONDURANT. Effects of oxygen breathing on the heart rate, blood pressure, and cardiac index of normal men resting with reactive hyperemia and after atropine. *J. Clin. Invest.* 41: 126, 1962.
72. DAMANT, G. C. C. Physiological effects of work in compressed air. *Nature* 126: 606, 1930.
73. DAUTREBANDE, L., AND J. S. HALDANE. The effects of respiration of oxygen on breathing and circulation. *J. Physiol., London* 55: 296, 1921.
74. DA VINCI, L. Selections from the original manuscripts. Naval warfare. Leic. 226, 1114 (in possession of Earl of Leicester, Holkham Hall).
75. DAVIS, R. H. *Deep Diving and Submarine Operations* (5th ed.). London: St. Catherine Press, 1951, chap. 7, p. 136.
76. DEJOURS, P., Y. LABROUSSE, J. RAYNAUD, F. GIRARD, AND A. TEILLAC. Stimulus oxygène de la ventilation au repos et au cours de l'exercice musculaire, à basse altitude (50 m), chez l'homme. *Rev. Franc. Etudes Clin. Biol.* 3(2): 105, 1958.
77. DELALLA, V., JR. Causes of skin cooling in pressure

breathing, deep inspiration and deep expiration. *Am. J. Physiol.* 152: 122–130, 1948.

78. DERN, R. J., AND W. O. FENN. The effect of varying pulmonary pressure on the arterial pressures in man and anesthetized cats. *J. Clin. Invest.* 26: 460, 1947.
79. DICKENS, F. The toxic effects of oxygen on brain metabolism and on tissue enzymes. II. Tissue enzymes. *Biochem. J.* 40: 171, 1946.
80. DONALD, K. W. Oxygen poisoning in man. I. *Brit. Med. J.* 1: 667, 1947.
81. DONALD, K. W. Oxygen poisoning in man. II. Signs and symptoms of oxygen poisoning. *Brit. Med. J.* 1: 712, 1947.
82. DONALD, K. W. Oxygen bends. *J. Appl. Physiol.* 7: 639–644, 1954–55.
83. DOUGHERTY, J. H., AND K. E. SCHAEFER. Adjustment of carbon dioxide stores in divers during voluntary hyperventilation. *Federation Proc.* 21: 441, 1962.
84. DRIPPS, R. D., AND J. H. COMROE, JR. The effect of the inhalation of high and low oxygen concentrations on respiration, pulse rate, ballistocardiogram and arterial oxygen saturation (oximeter) of normal individuals. *Am. J. Physiol.* 149: 277–291, 1947.
85. DUBOIS, A. B. Breath holding. *Natl. Acad. Sci. Natl. Res. Council Publ.* No. 377: 90, 1955.
86. DUBOIS, A. B., G. F. BOND, AND K. E. SCHAEFER. Alveolar gas exchange during submarine escape. *J. Appl. Physiol.* 18: 509–512, 1963.
87. DUFFNER, G. J. Medical problems involved in underwater compression and decompression. *Clinical Symposia, Ciba,* 10: 99, 1958.
88. DUFFNER, G. J. Recent studies of helium exchange in diving. In: *Man's Dependence on the Earthly Atmosphere*, edited by K. E. Schaefer. New York: Macmillan, 1962, p. 315.
89. DUFFNER, G. J., AND H. H. SNIDER. Effects of exposing men to compressed air and helium-oxygen mixtures for 12 hours at pressures of 2–2.6 atmospheres. Res. Rept. No. 1-59, U. S. Naval Experimental Diving Unit, Washington, D. C., 1958.
90. DWYER, J. V. Calculation of air decompression tables. Res. Rept. No. 4-56, U. S. Naval Experimental Diving Unit, Washington, D. C., 1955.
91. ECKENHOFF, J. E., J. H. HAFKENSCHIEL, AND C. M. LANDMESSER. The coronary circulation in the dog. *Am. J. Physiol.* 148: 582–596, 1947.
92. END, E. The use of new equipment and helium gas in a world record dive. *J. Ind. Hyg. Toxicol.* 20: 511, 1938.
93. FEATHERSTONE, R. M., C. A. MUEHLBAECHER, F. L. DEBON, AND J. A. FORSAITH. Interactions of inert anesthetic gases with proteins. *Anesthesiology* 22: 977, 1961.
94. FENN, W. O., AND L. E. CHADWICK. Effect of pressure breathing on blood flow through the finger. *Am. J. Physiol.* 151: 270–275, 1947.
95. FERRIS, E. B., JR., G. L. ENGEL, AND J. ROMANO. The clinical nature of high altitude decompression sickness. In: *Decompression Sickness*, edited by J. F. Fulton. Philadelphia: Saunders, 1951, p. 4.
96. FROEB, H. F. Ventilatory response of SCUBA divers to CO_2 inhalations. *J. Appl. Physiol.* 16: 8–10, 1961.
97. GAUER, O. H. Homeostasis of the extra-arterial circulation. In: *Man's Dependence on the Earthly Atmosphere*, edited by K. E. Schaefer. New York: Macmillan, 1962, p. 200.
98. GAUER, O. H., J. P. HENRY, H. O. SIEKER, AND W. E. WENDT. The effects of negative pressure breathing on urine flow. *J. Clin. Invest.* 33: 287, 1954.
99. GERBIS, H., AND R. KOENIG. *Drucklufterkrankungen (Caissonkrankheiten)*. Leipzig: Thieme, 1939.
100. GERSCHMAN, R. The biological effects of increased oxygen tension. In: *Man's Dependence on the Earthly Atmosphere*, edited by K. E. Schaefer. New York: Macmillan, 1962, p. 171.
101. GERSCHMAN, R., D. L. GILBERT, AND D. CACCAMISE. Effect of various substances on survival times of mice exposed to different high oxygen tensions. *Am. J. Physiol.* 192: 563–571, 1958.
102. GERSCHMAN, R., D. L. GILBERT, S. W. NYE, P. DWYER, AND W. O. FENN. Oxygen poisoning and X-irradiation: a mechanism in common. *Science* 119: 623, 1954.
103. GERSCHMAN, R., D. L. GILBERT, S. W. NYE, P. W. NADIC, AND W. O. FENN. Role of adrenalectomy and adrenal-hormones in oxygen poisoning. *Am. J. Physiol.* 178: 346–350, 1954.
104. GESELL, R. On the chemical regulation of respiration. I. The regulation of respiration with special reference to the metabolism of the respiratory center and the coordination of the dual function of hemoglobin. *Am. J. Physiol.* 66: 5–49, 1923.
105. GILBERT, D. S., R. GERSCHMANN, B. K. RUHM, AND W. E. PRICE. The production of hydrogen peroxide by high oxygen pressures. *J. Gen. Physiol.* 41: 989, 1958.
106. GOFF, L. G., AND R. G. BARTLETT, JR. Elevated end-tidal CO_2 in trained underwater swimmers. *J. Appl. Physiol.* 10: 203–206, 1957.
107. GOFF, L. G., H. G. BRUBACH, AND H. SPECHT. Measurements of respiratory responses and work efficiency of underwater swimmers utilizing improved instrumentation. *J. Appl. Physiol.* 10: 197–202, 1957.
108. GOLDING, F. C., P. GRIFFITHS, H. V. HEMPLEMAN, W. D. M. PATON, AND D. N. WALDER. Decompression sickness during construction of the Dartford tunnel. *Brit. J. Ind. Med.* 17: 167, 1960.
109. GREGG, D. E. Homeostasis of the arterial circulation. In: *Man's Dependence on the Earthly Atmosphere*, edited by K. E. Schaefer. New York: Macmillan, 1962, p. 216.
110. HALDANE, J. S. *Respiration*. New Haven: Yale Univ. Press, 1922.
111. HARVEY, E. N. Physical factors in bubble formation. In: *Decompression Sickness*, edited by J. F. Fulton. Philadelphia: Saunders, 1951, p. 90.
112. HARVEY, E. N. Animal experiments on bubble formation. I. Bubble formation in cats. In: *Decompression Sickness*, edited by J. F. Fulton. Philadelphia: Saunders, 1951, p. 115.
113. HAWKINS, J. A., C. W. SHILLING, AND R. A. HANSEN. A suggested change in calculating decompression tables for diving. *U. S. Naval Med. Bull.* 33: 327, 1936.
114. HAYMAKER, W. Decompression sickness. In: *Handbuch der speziellen pathologischen Anatomie und Histologie*, edited by W. Scholz. Berlin: Springer, 1957, Bd. 13, Teil 1, pp. 1600–1663.
115. HAYMAKER, W., AND A. D. JOHNSTON. Pathology of decompression sickness. A comparison of the lesions in airmen with those in caisson workers and divers. *Military Med.* 117: 285, 1955.
116. HELLER, R., W. MAGER, AND H. VON SCHRÖTTER.

Luftdruckerkrankungen mit besonderer Berücksichtigung der sogenannten Caisson Krankeit. Wien: Holder, 1900, pt. 2.

117. HEMPLEMAN, H. V. The resistance of animals to chronic oxygen poisoning. Medical Research Council, Royal Naval Personnel Research Committee, Rept. R.N.P. 51/652, U.P.S. 127, R.N.P.L. 1/51, 1951.
118. HEMPLEMAN, H. V. A new theoretical basis for the calculation of decompression tables. Medical Research Council, Royal Naval Personnel Research Committee, R.N.P.L. Rept. III, Part A. 52–708, 1952.
119. HEMPLEMAN, H. V. The unequal ratio of uptake and elimination of tissue nitrogen gas in diving procedures. Medical Research Council, Royal Naval Personnel Research Committee, R.N.P.L. Rept. 5, 1960.
120. HESSER, C. M. The role of nitrogen in breath holding at increased pressures. In: *Man's Dependence on the Earthly Atmosphere*, edited by K. E. Schaefer. New York: Macmillan, 1962, p. 327.
121. HILL, L. Compressed air and its physiological effects. *Notices Proc. Roy. Inst.* 18: 364, 1905–07.
122. HILL, L. *Caisson Sickness.* London: Longmans, Green, 1912.
123. HILL, L., AND J. J. MACLEOD. The influence of high pressure oxygen on the circulation of the blood. *J. Hyg.* 3: 401, 1903.
124. HILL, L., AND A. E. PHILLIPS. Deep sea diving. *J. Roy. Naval Med. Serv.* 18: 165, 1932.
125. HOFF, E. C. *A Bibliographical Sourcebook of Compressed Air, Diving and Submarine Medicine.* Washington, D. C.: Navy Dept., Bur. Med. Surg., 1948, 382 pp.
126. HOFF, E. C., AND L. J. GREENBAUM, JR. *A Bibliographical Sourcebook of Compressed Air, Diving and Submarine Medicine.* Washington, D. C.: Navy Dept., Bur. Med. Surg., 1954, vol. II.
127. HOLT, J. P. The effect of positive and negative intrathoracic pressure on peripheral venous pressure in man. *Am. J. Physiol.* 139: 208–211, 1942–43.
128. HORNUNG. Herzbefund bei Caissonarbeitern. *Muench. Med. Wochschr.* 48: 1444, 1901.
129. HYMAN, A., J. L. PATTERSON, T. W. DUKE, AND L. L. BATTEY. The cerebral circulation and metabolism in arteriosclerotic and hypertensive cerebrovascular disease. *New Engl. J. Med.* 249: 223, 1953.
130. IRVING, L. Changes in the blood flow through the brain and muscles during the arrest of breathing. *Am. J. Physiol.* 122: 207–214, 1938.
131. IRVING, L. The insensitivity of diving animals to CO_2. *Am. J. Physiol.* 124: 729–734, 1938.
132. IRVING, L. Respiration in diving mammals. *Physiol. Rev.* 19: 112–134, 1939.
133. IRVING, L., P. F. SCHOLANDER, AND S. W. GRINNELL. Significance of the heart rate to the diving ability of the seal. *J. Cellular Comp. Physiol.* 18: 283–297, 1941.
134. IRVING, L., P. F. SCHOLANDER, AND S. W. GRINNELL. The regulation of arterial blood pressure in the seal during diving. *Am. J. Physiol.* 135: 557–566, 1942.
135. JAVAL, A. Recherche sur la tension artérielle dans l'air compriné. *Compt. Rend. Soc. Biol.* 75: 413, 1913.
136. JOHANSEN, K., AND J. KROG. Peripheral circulatory response to submersion asphyxia in the duck. *Acta Physiol. Scand.* 46: 194–200, 1959.
137. JONES, H. B. Gas exchange and blood tissue perfusion factors in various body tissues. In: *Decompression Sickness*, edited by J. F. Fulton. Philadelphia: Saunders, 1951, p. 292.
138. KARSNER, H. T. The pathological effects of atmospheres rich in oxygen. *J. Exptl. Med.* 45: 865, 1927.
139. KARSNER, H. T., AND J. E. ASH. A further study of the pathological effects of atmospheres rich in oxygen. *Lab. Clin. Med.* 2: 254, 1916–17.
140. KAUNITZ, J. Myocardial damage resulting from high oxygen tension. *J. Aviation Med.* 13: 267, 1942.
141. KELLER, H. Grundlagen—Probleme der Dekompressionsbestimmung. *International Symposium on the Pathological Physiology of Diving*, Lisbon, 1961, pp. 22–27.
142. KETY, S. S., AND C. F. SCHMIDT. The effects of altered arterial tensions of CO_2 and O_2 on cerebral blood flow and cerebral O_2 consumption of normal young men. *J. Clin. Invest.* 27: 484, 1948.
143. KINSEY, J. L. Air embolism as a result of submarine escape training. *U. S. Armed Forces Med. J.* 5: 243, 1956.
144. KROGH, A. *The Comparative Physiology of Respiratory Mechanisms.* Philadelphia: Univ. Pennsylvania Press, 1941.
145. LAMBERTSEN, C. J. Respiratory and circulatory actions of high oxygen pressure. *Natl. Acad. Sci. Natl. Res. Council Publ.* No. 377: 39, 1955.
146. LAMBERTSEN, C. J., J. H. EWING, R. H. KOUGH, R. GOULD, AND M. W. STROUD 3RD. Oxygen toxicity. Arterial and internal jugular blood gas composition in man during inhalation of air, 100% O_2 and 2% CO_2 in O_2 at 3.5 atmospheres ambient pressure. *J. Appl. Physiol.* 8: 255–263, 1955.
147. LAMBERTSEN, C. J., R. H. KOUGH, D. V. COOPER, G. L. EMMEL, H. H. LOESCHCKE, AND C. F. SCHMIDT. Oxygen toxicity. Effects in man of oxygen inhalation at 1 and 3.5 atmospheres upon blood gas transport, cerebral circulation and cerebral metabolism. *J. Appl. Physiol.* 5: 471–486, 1953.
148. LAMBERTSEN, C. J., R. H. KOUGH, D. V. COOPER, G. L. EMMEL, H. H. LOESCHCKE, AND C. F. SCHMIDT. Comparison of relationship of respiratory minute volume to pCO_2 and pH of arterial and internal jugular blood in normal man during hyperventilation produced by low concentrations of CO_2 at 1 atmosphere and by O_2 at 3.0 atmospheres. *J. Appl. Physiol.* 5: 803–813, 1953.
149. LAMBERTSEN, C. J., S. G. OWEN, H. WENDEL, M. W. STROUD, A. A. LURIE, W. LOCHNER, AND G. F. CLARK. Respiratory and cerebral circulatory control during exercise at .21 and 2.0 atmospheres inspired pO_2. *J. Appl. Physiol.* 14: 966–982, 1959.
150. LAMBERTSEN, C. J., M. W. STROUD 3RD, J. H. EWING, AND C. MACK. Oxygen toxicity. Effects of oxygen breathing at increased ambient pressure upon pCO_2 of subcutaneous gas depots in men, dogs, rabbits and cats. *J. Appl. Physiol.* 6: 358–368, 1953.
151. LAMBERTSEN, C. J., R. W. STROUD 3RD, R. A. GOULD, R. H. KOUGH, J. H. EWING, AND C. F. SCHMIDT. Oxygen toxicity. Respiratory responses of normal men to inhalation of 6 and 100 per cent oxygen under 3.5 atmospheres pressure. *J. Appl. Physiol.* 5: 487–494, 1953.
152. LANPHIER, E. H. Use of nitrogen-oxygen mixtures in diving. *Natl. Acad. Sci. Natl. Res. Council Publ.* No. 377: 74, 1955.
153. LANPHIER, E. H. Nitrogen-oxygen mixture physiology,

phases 1 and 2. Res. Rept. No. 7-55, U. S. Naval Experimental Diving Unit, Washington, D. C., 1955.

154. LANPHIER, E. H. Carbon dioxide retention in working dives breathing nitrogen-oxygen mixtures at depth. *Federation Proc.* 15: 116, 1956.

155. LANPHIER, E. H. Nitrogen-oxygen mixture physiology, phases 4 and 6. Res. Rept. No. 7-58, U. S. Naval Experimental Diving Unit, Washington, D. C., 1958.

156. LANPHIER, E. H. Hazards and medical problems of skin and scuba diving. *Spectrum* 8: 156, 1960.

157. LANPHIER, E. H., AND R. A. MORIN. Effects of gas density on carbon dioxide elimination. *The Physiologist* 4(3): 63, 1961.

158. LANPHIER, E. H., AND H. RAHN. Gas exchange during simulated breath-hold dives. *Federation Proc.* 20: 424, 1961.

159. LARSON, H. E. A history of self-contained diving and underwater swimming. *Natl. Acad. Sci. Natl. Res. Council Publ.* No. 469, 1959.

160. LATHAM, F. The oxygen paradox. Experiments on the effects of oxygen in human anoxia. *Lancet* 1: 77, 1951.

161. LENNOX, W. G., AND A. R. BEHNKE, JR. Effect of increased oxygen pressure on the seizures of epilepsy. *Arch. Neurol. Psychiat.* 35: 782, 1936.

162. LEVY, E. Compressed air illness and its engineering importance, with a report of cases at the East River tunnels. *U. S. Bur. Mines Tech. Paper* No. 285: 1–46, 1922.

163. LIEBOW, A. A., J. E. STARK, J. VOGEL, AND K. E. SCHAEFER. Intrapulmonary air trapping in submarine escape training casualties. *U. S. Armed Forces Med. J.* 10: 265, 1959.

164. LUNDIN, G. Nitrogen elimination from the tissues during oxygen breathing and its relationship to the fat-muscle ratio and the localization of bends. *J. Physiol., London* 152: 167, 1960.

165. MACCLATCHIE, L. K. Medical aspects of submarine "lung" training. *U. S. Naval Med. Bull.* 29: 357, 1931.

166. MACHATTIE, L., AND H. RAHN. Survival of mice in absence of inert gas. *Proc. Soc. Exptl. Biol. Med.* 104: 772, 1960.

167. MACKAY, R. S. To determine the greatest depth in water at which one can breathe through a tube. *Am. J. Phys.* 16: 186, 1948.

168. MARÉCHAUX, E. W. Über die Wirkung von Sauerstoff erhöhten Teildruckes auf lungengeschädigte Tiere. *Arch. Exptl. Pathol. Pharmakol.* 201: 213, 1943.

169. MARQUORT, W., AND J. RIETZ. Physiologische Untersuchungen und Beobachtungen an Druckluftarbeitern. *Z. Ges. Exptl. Med.* 106: 684, 1939.

170. MARSHALL, R., E. H. LANPHIER, AND A. B. DUBOIS. Resistance to breathing in normal subjects during simulated dives. *J. Appl. Physiol.* 9: 5–10, 1956.

171. MASLAND, R. L. Review of cases of collapse occurring in altitude chambers. *Natl. Acad. Sci. Natl. Res. Council Comm. Aviation Med. Rept.* No. 179, 1943.

172. MATTHES, K. Herz- und Kreislauf bei Atmosphärischem Unterdruck und Überdruck, In: *Handbuch der Inneren Medizin* (4 Aufl.) edited by G. v. Bergmann, W. Frey, and H. Schwiegk. Berlin: Springer, 1960, Bd. IX, pt. 4. p. 1–58.

173. MEAD, J. Resistance to breathing at increased ambient pressures. *Natl. Acad. Sci. Natl. Res. Council Publ.* No. 377: 112, 1955.

174. MEAD, J. Measurement of inertia of the lungs at increased ambient pressure. *J. Appl. Physiol.* 9: 208–212, 1956.

175. MEDA, E. I. Richerche elettro cardiografiche durante la respirazione di miscele ricche di ossiggeno. *Riv. Med. Aeron.* 13: 441, 1950.

176. MEDA, E. I. Effetti della respirazione di miscele ricche di O_2 sull'apparato cardiovascolare dell'uomo. II. Variazione elettrocardiografiche nell'uomo durante la respirazione di O_2. *Boll. Soc. Ital. Biol. Sper.* 26: 931, 1950.

177. MICHEL, E. L., R. W. LANGEVIN, AND C. F. ~~SELL~~ Effect of continuous human exposure to oxygen tensions of 418 mm Hg for 169 hours. *Aerospace Med.* 31: 138, 1960.

178. MILES, S. Oxygen syncope. Medical Research Council, Royal Naval Personnel Research Committee, Rept. R.N.P. 57/880, U.P.S. 161, 1957.

179. MILES, S. Respiratory patterns of 100 divers. Effects of hypoxia and carbon dioxide. Medical Research Council, Royal Naval Personnel Research Committee, Rept. R.N.P. 57/888, U.P.S. 164, R.N.P.L. 4/57, 1957.

180. MILES, S. The effect of increase in barometric pressure on maximum breathing capacity. Medical Research Council, Royal Naval Personnel Research Committee, Rept. R.N.P. 58/922, U.P.S. 174, R.N.P.L. 1/58, 1958.

181. MILIC-EMILI, J., AND J. M. TYLER. Relationship between arterial pCO_2 and work of breathing in man. *Federation Proc.* 21: 445, 1962.

182. MOXON, W. Influence of the circulation upon the nervous system. *Lancet* 1: 527, 1881.

183. MURDAUGH, N. V., JR., W. L. MITCHELL, J. C. SEABURY, AND H. O. SIEKER. Volume receptors and post-prandial diuresis in the seal. *Proc. Soc. Exptl. Biol. Med.* 108: 16, 1961.

184. NIMS, L. F. Environmental factors affecting decompression sickness. Pt. 1. A physical theory of decompression sickness. In: *Decompression Sickness*, edited by J. F. Fulton. Philadelphia: Saunders, 1951, chap. VIII, pp. 192–222

185. NOELL, W. K. Visual cell effects of high oxygen pressures. *Federation Proc.* 14: 107, 1955.

186. NOELL, W. K. Effects of high and low oxygen tension on the visual system. In: *Environmental Effects on Consciousness*, edited by K. E. Schaefer. New York: Macmillan, 1962, p. 3.

187. OLIVER, T. The physiology and pathology of work in compressed air. *Lancet* 1: 638, 1909.

188. ORR, J. B., AND A. WATSON. Study of the respiratory mechanism in the duck. *J. Physiol., London* 46: 337, 1913.

189. ORZECHOWSKI, G., AND K. HOLSTE. Sauerstoffvergiftung. *Arch. Exptl. Pathol. Pharmakol.* 190: 198, 1938.

190. PAPPENHEIMER, J. R. Environmental factors affecting capillary exchange. In: *Man's Dependence on the Earthly Atmosphere*, edited by K. E. Schaefer. New York: Macmillan, 1962, p. 189.

191. PATON, W. D. M., AND D. N. WALDER. *Compressed Air Illness* (Medical Research Council, Special Rept. Ser. No. 281). London: H. M. Stationery Office, 1954.

192. PAULING, L. A molecular theory of general anesthesia. *Science* 134: 15–21, 1961.

193. PEIRANO, J. H., H. J. ALVIS, AND G. J. DUFFNER. Submarine escape training experience; summary of twenty-five year period. BUMED Proj. NM 002 015 08, Rept. No. 3, 1955.

194. PENROD, K. E. Nature of pulmonary damage produced by high oxygen pressures. *J. Appl. Physiol.* 9: 1–4, 1956.
195. PFEIFFER, C. C., AND J. GERSCH. Prevention of convulsions of oxygen poisoning by means of drugs. U. S. Naval Medical Research Institute Proj. X-192, Rept. No. 2, 1944.
196. PHILLIPS, A. E. Recent research work in deep sea diving. *Proc. Roy. Soc. Med.* 25: 692, 1931.
197. POLAK, B., AND H. ADAMS. Traumatic air embolism in submarine escape training. *U. S. Naval Med. Bull.* 30: 165, 1932.
198. PUGH, L. G. C. E. The effect of acute and chronic exposure to low oxygen supply on consciousness. In: *Environmental Effects on Consciousness*, edited by K. E. Schaefer. New York: Macmillan, 1962, p. 106.
199. RASHBASS, C. Investigation into the decompression tables. v. 1. Royal Naval Personnel Research Committee, Rept. R.N.P. 55/847, U.P.S. 151 D.P. 14, 1955.
200. RASHBASS, C. The unimportance of carbon dioxide as a cause of nitrogen narcosis. Medical Research Council, Royal Naval Personnel Research Committee, Rept. 55/854, U.P.S. 153, 1955.
201. RASHBASS, C., AND W. J. EATON. The effect of oxygen concentration on the occurrence of decompression sickness. Royal Naval Personnel Research Committee, Rept. R.N.P. 57/897, U.P.S. 169, 1957.
202. REMBOLT, S. Ueber die Wirkung der Caissonarbeit auf den Organismus. *Med. Korrespondenzbl. Württemberg* 65: 249, 1895.
203. RICHARDS, D. W., AND A. L. BARACH. Prolonged residence in high oxygen atmospheres. Effects on normal individuals and on patients with chronic cardiac and pulmonary insufficiency. *Quart. J. Med.* 3: 437, 1934.
204. RODBARD, S. Recurrence of decompression sickness on re-ascent to high altitudes. *Air Surgeon's Bull.* 1: 6–7, 1944.
205. ROGER, A., P. CABARROA, AND H. GASTAUT. E.E.G. changes in humans due to changes in surrounding atmospheric pressure. *Electroencephalog. Clin. Neurophysiol.* 7: 152, 1955.
206. RUFF, S., AND H. STRUGHOLD. *Grundriss der Luftfahrtmedizin.* Leipzig: Barth, 1939, p. 153.
207. SANGER, C. G., G. G. NAHAS, A. R. GOLDBERG, AND G. M. D'ALESSIO. Effects of 2-amino-2 hydroxymethyl-1-3 propanediol on oxygen toxicity in mice. *Ann. N. Y. Acad. Sci.* 92: 711, 1961.
208. SCHAEFER, K. E. Atmung und Sauerebasengleichgewicht bei langdauerndem Aufenthalt in 3% CO_2. *Arch. Ges. Physiol.* 251: 689, 1949.
209. SCHAEFER, K. E. The role of carbon dioxide in the physiology of human diving. *Natl. Acad. Sci. Natl. Res. Council Publ.* No. 377: 131–139, 1955.
210. SCHAEFER, K. E. Oxygen toxicity studies in underwater swimming. *J. Appl. Physiol.* 8: 524–531, 1955–56.
211. SCHAEFER, K. E. Respiratory pattern and respiratory response to CO_2. *J. Appl. Physiol.* 13: 1–14, 1958.
212. SCHAEFER, K. E. Time concentration relationship in adaptation to CO_2. *Proc. Intern. Physiol. Congr., 21st, Buenos Aires, Abstr. Commun.* 1959, p. 245.
213. SCHAEFER, K. E. Blood pH and pCO_2 homeostasis in chronic respiratory acidosis related to the use of amine and other buffers. *Ann. N. Y. Acad. Sci.* 92: 401, 1961.
214. SCHAEFER, K. E. A concept of triple tolerance limits based on chronic carbon dioxide toxicity studies. *Aerospace Med.* 32: 197, 1961.
215. SCHAEFER, K. E. Adaptation to skin diving. *Federation Proc.* 20: 215, 1961.
216. SCHAEFER, K. E. Central nervous system effects of CO_2. In: *Selective Vulnerability of the Brain in Hypoxaemia*, edited by J. P. Schadé and McMenerney. Oxford: Blackwell, 1963, pp. 101–123.
217. SCHAEFER, K. E. Effects of carbon dioxide on consciousness. In: *Environmental Effects on Consciousness*, edited by K. E. SCHAEFER. New York: Macmillan, 1962, p. 96.
218. SCHAEFER, K. E., AND H. J. ALVIS. The effect of inhalation of low oxygen concentration (10.5% O_2 in N_2) over a period of 33 minutes on respiration, pulse rate, arterial oxygen saturation (oximeter) and oxygen uptake. *U. S. Naval Med. Res. Lab. Rept.* No. 175, 10: 76, 1951.
219. SCHAEFER, K. E., AND C. R. CAREY. Alveolar pathways during 90-foot breath-hold dives. *Science* 137: 1051–1052, 1962.
220. SCHAEFER, K. E., E. R. CORNISH, JR., C. A. LUKAS, AND C. R. CAREY. Respiration and circulation during and after inhalation of various concentrations of carbon dioxide. *U. S. Naval Med. Res. Lab. Rept.* No. 189, 11(6), 1952.
221. SCHAEFER, K. E., W. P. MCNULTY, JR., C. R. CAREY, AND A. A. LIEBOW. Mechanisms in development of interstitial emphysema and air embolism on decompression from depth. *J. Appl. Physiol.* 13: 15–29, 1958.
222. SCHAEFER, K. E., G. NICHOLS, JR., R. C. STROUD, AND C. R. CAREY. Pulmonary gas exchange and blood gas transport during and after skin diving to 90 feet. *Federation Proc.* 17: 141, 1958.
223. SCHOLANDER, P. F. Experimental investigations on the respiratory function in diving mammals and birds. *Hvalradets Skrifter Norske Videnskaps-Akad. Oslo* No. 22, 1940, 131 pp.
224. SCHOLANDER, P. F., H. T. HAMMEL, H. LEMESSURIER, E. HEMMINGSEN, AND W. GAREY. Circulatory adjustment in pearl divers. *J. Appl. Physiol.* 17: 184–190, 1962.
225. SCHOLANDER, P. F., L. IRVING, AND S. W. GRINNELL. Aerobic and anaerobic changes in the seal muscles during diving. *J. Biol. Chem.* 142: 431–440, 1942.
226. SEELKOPF, K., AND R. VON WERZ. Über die Rolle der Kohlensäure bei der Sauerstoffvergiftung. *Arch. Exptl. Pathol. Pharmakol.* 205: 351–366, 1948.
227. SEUSING, J., AND H. C. DRUBE. Die Bedeutung der Hyperkapnie für das Auftreter des Tiefenrausches. *Klin. Wochschr.* 38: 1088, 1960.
228. SHAW, L. A., A. R. BEHNKE, A. C. MESSER, R. M. THOMSON, AND E. P. MOTLEY. The equilibrium of the gaseous nitrogen in the dog's body following changes of nitrogen tension in the lungs. *Am. J. Physiol.* 112: 545–553, 1935.
229. SHILLING, C. W., R. A. HANSEN, AND J. A. HAWKINS. The effect of increased air pressure on vital capacity, expiratory force and breath-holding ability. *Am. J. Physiol.* 110: 616–619, 1935.
230. SHILLING, C. W., J. A. HAWKINS, AND R. A. HANSEN. The influence of increased barometric pressure on the pulse rate and arterial blood pressure. *U. S. Naval Med. Bull.* 35: 39, 1936.
231. SHILLING, C. W., AND W. W. WILLGRUBE. Quantitative study of mental and neuromuscular reactions as influenced

by increased air pressure. *U. S. Naval Med. Bull.* 35: 373, 1937.

232. SICKER, H. O., O. H. GAUER, AND J. P. HENRY. The effect of continuous negative pressure breathing on water and electrolyte excretion by the human kidney. *J. Clin. Invest.* 33: 572, 1954.
233. SMITH, A. H. *Physiology, Pathology and Therapeutic Effects of Compressed Air.* Detroit: Davis, 1886.
234. SMITH, F. J. C., G. A. BENNETT, J. W. HEIM, R. M. THOMSON, AND C. K. DRINKER. Bodily changes and development of pulmonary resistance in rats living under compressed air conditions. *J. Exptl. Med.* 56: 63, 1932.
235. SMITH, F. J. C., G. A. BENNETT, J. W. HEIM, R. M. THOMSON, AND C. K. DRINKER. Morphological changes in the lungs of rats living under compressed air conditions. *J. Exptl. Med.* 56: 79, 1932.
236. SOULIE, P. Modifications expérimentales de la résistance individuelle de certains animaux à l'action toxique de l'oxygène. *Compt. Rend. Soc. Biol.* 130: 541, 1939.
237. STADIE, W. C., B. C. RIGGS, AND N. HAUGAARD. Oxygen poisoning III. The effect of high oxygen pressures upon the metabolism of brain. *J. Biol. Chem.* 160: 191, 1945.
238. STADIE, W. C., B. C. RIGGS, AND N. HAUGAARD. Oxygen poisoning IV. The effect of high oxygen pressures upon the metabolism of liver, kidney, lung, and muscle tissue. *J. Biol. Chem.* 160: 209, 1945.
239. STELZNER, H. *Tauchertechnik.* Lubeck, Germany: Coleman, 1943.
240. STIGLER, R. Die physiologische Bedeutung von Differenzen zwischen extra- und intrathorakalem Drucke. *Zentr. Physiol.* 25: 1095, 1911.
241. TAYLOR, H. J. The effect of breathing oxygen at atmospheric pressure on tissue oxygen and carbon dioxide tensions. *J. Physiol., London* 108: 264–269, 1949.
242. TAYLOR, H. J. The role of carbon dioxide in oxygen poisoning. *J. Physiol., London* 109: 272–280, 1949.
243. TING, E. Y., S. K. HONG, AND H. RAHN. Cardiovascular responses of man during negative-pressure breathing. *J. Appl. Physiol.* 15: 557–560, 1960.
244. TURNER, J., C. J. LAMBERTSEN, S. G. OWEN, H. WENDEL, AND H. CHIODI. Effects of .08 and .8 atmospheres of inspired pO_2 upon cerebral hemodynamics at a "constant" alveolar pCO_2 of 43 mm Hg. *Federation Proc.* 16: 130, 1957.
245. VAN DER AUE, O. E., R. J. KELLER, E. S. BRINTON, G. BARRON, H. D. GILLIAM, AND R. J. JONES. Calculation and testing of decompression tables for air dives employing the procedure of surface decompression and the use of oxygen. Res. Rept. No. 1, U. S. Naval Experimental Diving Unit, Washington, D. C., 1951.
246. VAN GOOR, H., AND J. JONGBLOED. Oxygen poisoning. *Enzymologia* 13: 313–324, 1949.
247. VAVALA, D. A. Present status of aeroembolism. *J. Aviation Med.* 26: 230, 1955.
248. VIVENOT, R., JR. Ueber die Veränderungen im arteriellen Stromgebiete unter dem Einflusse des verstärkten Luftdruckes. *Arch. Pathol. Anat. Physiol.* 34: 515, 1865.
249. WAGNER, C. E. Observations of gas bubbles in pial vessels of cats following rapid decompression from high pressure atmospheres. *J. Neurophysiol.* 8: 29–32, 1945.
250. WHITEHORN, W. V., A. EOELMANN, AND F. A. HITCHCOCK. The cardiovascular responses to the breathing of 100 per cent oxygen at normal barometric pressure. *Am. J. Physiol.* 146: 61–65, 1946.
251. WHITEHORN, W. V., A. LEIN, AND A. EDELMANN The general tolerance and cardiovascular responses of animals to explosive decompression. *Am. J. Physiol.* 147: 289–298, 1946.
252. WORKMAN, R., G. F. BOND, AND W. MAZZONE. Prolonged exposure of animals to pressurized, normal and artificial atmospheres. *U. S. Naval Med. Res. Lab. Rept.* No. 374, 1962.
253. WUENSCHE, O. Zur Pathogenese und Prophylaxe der Druckfall krankeit des Hoehenfliegers. 3. Intravasale Gasblasenbildung in Druckstürz versuch nach Hoehenakkomodation. *Intern. Z. Angew. Physiol.* 18: 165, 1960.
254. WUENSCHE, O., AND H. HARTMANN. Zur Pathogenese und Prophylaxe der Druckfallkrankeit des Hoehenfliegers. 4. Die Beeinflussung der intravasalen Gasblasenbildung nach rascher Dekompression durch Aenderung der Blutviscositaet. *Intern. Z. Angew. Physiol.* 18: 456, 1961.
255. YARBROUGH, O. D., W. WELHAM, E. S. BRINTON, AND A. R. BEHNKE. Symptoms of oxygen poisoning and limits of tolerance at rest and at work. Res. Rept. No. 1, U. S. Naval Experimental Diving Unit, Washington, D. C., 1947.
256. ZETTERSTROM, A. Deep sea diving with synthetic gas mixtures. *Military Surgeon* 103: 104, 1948.

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This report was prepared as an up-to-date, authoritative review article to cover the rapidly expanding field of diving and pressure physiology. It discusses cardiovascular and respiratory functions and adaptations in skin diving; hazards of skin diving and related adaptive changes; carbon dioxide intoxication and adaptation in diving; anoxia; oxygen toxicity; nitrogen narcosis; air embolism; and decompression sickness.

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