PHYSIOLOGICAL REVIEWS

VOL. 25 JANUARY, 1945 No. 1

EFFECTS OF OXYGEN AT INCREASED PRESSURE

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Shortly after having isolated O_2 Priestley (1775) wrote, "From the greater strength and vivacity of the flame of a candle, in this pure air, it may be conjectured, that it might be peculiarly salutary to the lungs in certain morbid cases . . . . But, perhaps, we may also infer from these experiments, that though pure dephlogisticated air might be very useful as a *medicine*, it might not be so proper for us in the usual healthy state of the body: for, as a candle burns out much faster in dephlogisticated than in common air, so we might, as may be said, *live out too fast*, and the animal powers be too soon exhausted in this pure kind of air. A moralist, at least, may say, that the air which nature has provided for us is as good as we deserve. . . . The feeling of it to my lungs was not sensibly different from that of common air; but I fancied that my breast felt peculiarly light and easy for some time afterwards. Who can tell but that, in time, this pure air, may become a fashionable article in luxury. Hitherto only two mice and myself have had the privilege of breathing it."

The study of the influence of O_2 on the animal organism and the view that while O_2 could be used to advantage therapeutically such use might be attended with some danger, had its inception, then, in the experiments of Priestley. But it is Lavoisier who is not infrequently credited with having been the first to recognize the possible nocuous effects of breathing O_2. The reason, for this, may perhaps be found in an erroneous interpretation which he made as a result of his having fallen into the company of physiologists. At least Foster (1901) suggests it was the association with Seguin which was responsible for Lavoisier's conclusion that the site of oxidations in the body was the lungs. This misinterpretation persisted tenaciously in spite of the evidence and argument to the contrary presented by a number of investigators, even for some time after the epoch-making blood gas studies of Magnus in 1837 which showed that the site of oxidations must be in the tissues as Mayow had maintained more than a century and a half before.

It is not surprising, therefore, that the belief should have arisen that increasing concentration of this incendiary substance in the lung caused severe pulmonary damage. Later experimental findings served to temper the more extreme of these interpretations and after a few cyclic swings the pendulum of opinion seemed to have reached a position of stability pointing to a goodly amount of evidence that breathing pure O_2 or hyperoxygenated air will cause not only general physiological

changes, but also pathological alterations. In very recent years numerous reports based largely on extensive use of O_2 on human subjects have appeared which maintain that the nocuous effects induced in experimental animals by O_2 has been overemphasized and that breathing O_2 in high concentrations at atmospheric pressure is relatively harmless. The available evidence does appear to indicate that men may be somewhat superior to mice—at least in their ability to withstand the deleterious effects of breathing O_2—but this does not dismiss O_2 as innocuous.

Naturally enough by far the greater part of the literature and investigative work concerning the effects of O_2 has been confined to increased O_2 tensions at atmospheric pressure. But the increasingly high pressure conditions to which man has found, and in the future is likely to find it expedient to expose himself either for industrial or therapeutic purposes, has called for a consideration of the effects of O_2 at tensions distinctly in excess of that equivalent to one atmosphere.

Increased O_2 tension in a respiratory gas may be attained by several methods: (1) by the use of either hyperoxygenated air or pure O_2 at normal barometric pressure, thus providing O_2 tensions up to that equivalent to 100 per cent of one atmosphere; (2) by the use of normal air under compression, in which case O_2 tensions in excess of one atmosphere may be attained; (3) by the use of hyperoxygenated air or pure O_2 under increased pressure which provides another means of attaining very high O_2 tensions. There is no sharp line of demarcation between the effects of O_2 tensions just below 760 mm. Hg and those above 760 mm. Hg but tensions of O_2 much in excess of this do introduce factors not operative to an appreciable extent where the O_2 tension is less than 760 mm. Hg. In addition to this, the fact that a desired increase in O_2 has been achieved in so many experimental investigations by the compression of normal or hyperoxygenated air, calls for a consideration of some of the possible complicating influences which such methods introduce. For these reasons, and as a matter of convenience, the material covered below is presented under the following main headings: I. Effects of Increased Oxygen Tensions Not in Excess of One Atmosphere, as Induced by Pure Oxygen, Hyperoxygenated Air or Normal Air at Increased Pressures; II. Possible Complicating Variables Introduced by Compressed Air or Artificial Gas Mixtures; III. Effects of Oxygen Tensions in Excess of One Atmosphere as Induced by Pure Oxygen, Hyperoxygenated Air, or Normal Air at High Pressure. The oxygen tensions considered in Part III will be referred to as oxygen at high pressure (OHP).

I. Effects of increased oxygen tensions not in excess of one atmosphere, as induced by pure oxygen, hyperoxygenated air, or normal air at increased pressures. *Metabolism.* Seguin and Lavoisier (1789) performed experiments from which they concluded that breathing pure O_2 did not alter any of the vital processes; the respiration and circulation were neither accelerated nor retarded and the temperature remained unchanged. These results were supported by the experiments of Regnault and Reiset (1849) in which animals (rabbit and dog) breathing O_2 in concentrations of from 46.63 per cent to 72.38 per cent for as long as 23 hours showed no change either in the O_2 consumption or in the respiratory quotient from that obtaining under normal conditions.

Birch (1859) reported, however, that the temperature of healthy animals was usually first increased then decreased while breathing O_2. Clinical observation, he thought, afforded evidence that O_2 when employed in disease might raise or lower the temperature under different circumstances but that only in rare instances did it exert any influence on persons enjoying perfect health. Smith (1870) disagreed with the finding of Regnault and Reiset and reported that in experiments upon himself there was an initial decrease in CO_2 exhaled, yet he was of the opinion that ultimately there was a slight increase in the CO_2 output. His short administrations of O_2 raise the question of the validity of his results.

The studies of Speck (1879) made on men, led him to support the conclusions of Regnault and Rieset. Lukjanow's data (1884) obtained from rat, cat, dog, guinea pig, dove and canary showed considerable variation; in many instances the O_2 uptake in O_2 rich atmospheres was increased but more than half of the experiments showed either no change or a decrease. His data are not convincing but they were interpreted as confirming the view of Regnault and Rieset. Saint-Martin (1884) on equally questionable data arrived at a similar conclusion that the chemical phenomena of respiration were not appreciably changed by breathing hyperoxygenated air. Wood and Cerna (1890) also claimed that the breathing of O_2 was without effect on the organism but in view of their limited number of experiments and the manner of O_2 administration such claim would appear to be hardly justified, especially where small changes may be involved.

Bert (1878) using methods similar to those of Regnault and Reiset found that when the animals were breathing O_2 mixtures equivalent to 48.7 per cent, their O_2 consumption was higher than when breathing mixtures of either higher or lower O_2 content (87.5 per cent and 20.96 per cent respectively). This led him to the conclusion that there was an optimum O_2 percentage for oxidations. "L'activité des combustions organiques a donc été en augmentant d'abord, pour diminuer ensuite après avoir passé un certain maximum qui est probablement placé au-dessus de 2 atmosphères."

Quinquaud (1884), interested in the therapeutic use of O_2, carried out a number of experiments chiefly on dogs; in most of these the O_2 was inspired from a balloon and expired into the free air (or into another balloon if analyses were desired). From these studies, and from a comparison of the gas content of arterial and venous bloods he drew the following conclusions: that it is possible to superoxygenate the blood by breathing pure O_2 so that an additional 2.2 volumes per cent is carried in arterial blood; that as a result of such O_2 breathing, there is a decrease in rectal temperature, a slight decrease in CO_2 exhaled, a diminution of organic combustion; and that O_2 has a sedative effect. These changes, he said, were analogous to, but less accentuated than those observed by Bert.

Fredricq (1884) reported that in experiments performed on himself and on rabbits there was no increase in the O_2 consumption when O_2 rich mixtures were breathed, but with O_2 poor mixtures, it was diminished. No data are given in his report, but he emphasizes that when the subject is changed from breathing ordinary air to O_2 enriched air, or to pure O_2, there occurs during the first few minutes an augmentation in the absorption of O_2 due to its solution in the blood and lymph, but after equilibrium is attained between plasma and pulmonary air, the

absorption of O_2 returns to its normal value, a conclusion which had been previously arrived at by Speck.

Some few years later Loewy (1894) concluded from his experiments that the respiratory gas exchange is independent (within wide limits) of the O_2 content of the respired air. Doubling the normal O_2 content of inspired air or decreasing it even to a point where an alveolar tension of 40 mm. Hg was attained, did not change the O_2 consumption or the CO_2 exhaled. In summarizing the results of his experiments in which the O_2 content of the inspired air had been increased to 37.7 per cent and 49.26 per cent, he reported that the metabolism was not altered, and the O_2 consumption showed no notable difference from normal. He disagreed with Bert's observations concerning an optimum O_2 percentage for oxidations.

Terray (1897) likewise reported that breathing of O_2 rich atmospheres did not appreciably alter the total metabolism of experimental animals and that with O_2 percentages of from 10.5 to 87, the metabolism was independent of the O_2 content of the air breathed; but along with his conclusion that metabolism was unchanged, Terray reported that the CO_2 output was diminished to some degree.

The consensus of opinion at about that time (Tigerstedt, 1902) was that breathing O_2 or hyperoxygenated air did not alter metabolism but an examination of the data presented by some investigators in support of that opinion reveals that the experimental evidence was not as convincing as was implied.

Rosenthal (1898, 1902) reported that breathing of O_2 rich mixtures caused a distinct and quite large increase in the uptake of O_2 and that there was a storage of O_2 in the tissues. These surprising results and conclusions were refuted by Durig (1903) and Schaternikoff (1904) who, apparently stimulated by Rosenthal's claims, had been working independently and with different methods in Vienna and Moscow respectively. Durig's experiments on both animals and men gave him data which led him to conclude that the O_2 consumption was not increased by breathing hyperoxygenated air and he found no evidence of O_2 storage in the tissues. Schaternikoff, in an attempt to determine if Rosenthal's claims, which had been arrived at by the use of small experimental animals, held also for man, was likewise unable to find any indication that the O_2 consumption was dependent upon the O_2 content of the inspired air.

Hill and Macleod (1902a), referring particularly to the reports of Panum (1868) and von Liebig (1878) that increase of atmospheric pressure had no distinct influence on the O_2 uptake or CO_2 output in man, and the report of L. Smith (1897a) that the O_2 tension in the blood was lowered by prolonged breathing in an atmosphere of pure O_2, remarked that the data up to that time were such that "Nothing conclusive can be asserted as to the influence of O_2 on the gaseous metabolism." Their own experiments, however (Hill and Macleod, 1902a, 1903c), showed that breathing pure O_2 at atmospheric pressure caused a decrease in the CO_2 exhaled and in the O_2 absorbed and a drop in body temperature. These changes did not occur immediately but were usually quite distinct in 30 minutes. It was concluded that breathing O_2 does cause a distinct diminution in metabolism.

The same investigators (Hill and Macleod, 1903a, b, c) found that compressed

air at 4 atmospheres and upwards also diminished the CO_2 output and lowered the body temperature and that these effects were most pronounced at the higher pressures. The British Admiralty report (Hill, 1912) indicated that the CO_2 output in divers during rest was not altered by breathing compressed air; the resting output in one subject was the same at a depth of 210 feet as it was at 6 feet. Hill and Macleod (1903c) state, "We observed like Bert that prolonged exposure to even one atmosphere of pure oxygen slightly lowered the CO_2 output and temperature of mice, both returning to normal on replacing the oxygen with air. On increasing the tension of O_2 we find a general increase in toxic effect, but no constant relationship owing to differences in individual susceptibility of mice." But these authors could not confirm Bert's conclusion that compressed air diminished the CO_2 output in proportion to the contained partial pressure of O_2, and they suggested there were factors, other than the partial pressure of O_2, to be considered, such as the cooling effect of compressed air due to its increased conductivity and saturation with water vapour, the increased resistance offered to movement of air through the respiratory passages and the altered diffusion of CO_2 from the alveolar air. However, the finding that the body temperature was lowered, was taken as clear proof by these investigators that the lowered CO_2 output was due to a decrease in oxidation rather than to any interference with release of CO_2 into the alveoli which might be caused by possible alteration in lung epithelium.

Hough (1910), in experimental studies carried out on human subjects breathing O_2 in 60 to 80 per cent mixtures, questioned the "soundness of the usual view that the consumption of oxygen by the cell is determined entirely by the cell and is independent of the quantity of oxygen provided by the blood." Benedict and Higgins (1911) felt that while the reports up to that time favored the view that increased O_2 in the respired air does not significantly alter metabolism, they were not entirely convincing and maintained that the question was "not yet definitely settled." In an attempt to get more detailed and reliable data these authors carried out a very careful experimental study on healthy men. Their determinations were made with the experimental subjects lying at complete muscular rest 12 hours after the last meal. The O_2 concentrations employed were 40, 60 and 90 per cent mixtures in air, but the duration of administration was relatively short, usually not more than 15 minutes, so that the full effects of the increased O_2 may not have had time to develop in every instance. The results of these tests led to the conclusion that when breathing the O_2 enriched air, the metabolism, as indicated by the gaseous exchange and respiratory quotient, was the same as that obtaining in ordinary air. However, in three of six subjects the O_2 consumption was found to be greater in the 40 per cent mixture than in either the higher (60 to 90 per cent) or the lower (20 per cent) O_2 mixtures; in one of these, the O_2 consumption in the 40 per cent mixtures was 3 per cent above that of the same subject in the 20 per cent mixture. The authors considered these increased O_2 consumptions insignificant, and while they pointed out that such effects were in agreement with the report of Bert that the optimum of O_2 consumption was in the neighborhood of 45 per cent mixture, they did not believe their results substantiated Bert's views.

Hill (1912c) maintained Bert's experiments were quite insufficient to justify his claim that O_2 consumption increased with an increase in O_2 content of the air breathed up to an optimum of about 45 per cent. Krogh (1916) likewise says Bert's results are invalid because his methods were not nearly accurate enough to demonstrate this. While admitting the determinations of Benedict and Higgins (1911) as probably the most accurate, Krogh does not fully agree with their conclusions, and maintains that if due consideration be given to the washing out of the tissues by nitrogen it "seems" that "breathing of oxygen does increase the metabolism to some slight extent, and it must be borne in mind that a large effect is not in any case to be expected, because the oxygen supply to the tissues will only be increased by the extra amount of oxygen physically dissolved in the arterial blood which cannot be more than 10 per cent of the total quantity carried. . . . The results obtained on warm-blooded animals point, when considered in their entirety, in the opinion of the writer, towards the conclusion that oxygen pressure is practically the limiting factor for the oxidations, but that it is so regulated as to be just sufficient. A diminution of the oxygen supply to the tissues, which will take place when the oxygen pressure in the inspired air falls below something like 85 mm., causes a decrease in rate of oxidation, while an increase in oxygen pressure appears to produce a slight increase."

Campbell (1927) found that the metabolism of rabbits was not altered by their prolonged exposure (about six weeks) to air in which the O_2 content was 200 per cent above normal and the barometric pressure at 750 mm. The O_2 consumption remained unchanged, but the O_2 and CO_2 tensions of the tissue, as estimated by intra-abdominal and subcutaneous bubble technique, increased. The body weight decreased during the O_2 exposure but gradually returned to normal after the animals' return to breathing normal air. Clark, Gaddie and Stewart (1933) obtained experimental data from isolated frogs' hearts which indicated that the R.Q. of hearts kept in O_2 instead of air, was greatly reduced thereby; the carbohydrate consumption slightly diminished and the total O_2 consumption was raised about 15 per cent.

Behnke, Johnson, Poppen and Motley (1935) reported that the O_2 consumption of healthy men is high during the first twenty minutes of exposure to 79 per cent O_2 at one atmosphere, then decreases to a constant level which is maintained for periods up to four hours. An inspection of their data shows that even after this period, the O_2 consumption level was still above the calculated basal rate. Richards and Barach (1934) found that the metabolic rate of two normal young men (measured by CO_2 output) was unchanged by a week's residence in an atmosphere enriched to 40 per cent of O_2.

Becker-Freyseng and Clamann (1939) observed a tendency to lowering of their body temperatures during the first 24 hours of exposure to 90 per cent O_2 at atmospheric pressure, but during the second day the body temperature increased—perhaps secondarily to the lung injury which the exposure induced rather than as the result of some more direct action of O_2 metabolism. The same authors also found changes in alveolar CO_2 tension; during the first hour it increased above normal, by the second hour it had decreased very distinctly, and except for a temporary rise at about the fifth hour it was well below normal for ten

hours of exposure. Anthony (1940) is of the opinion that breathing O_2 causes no change in metabolic rate.

Davis (1941) finding that the administration of O_2 caused an increase in the amount of carbon dioxide in the blood of normal, anesthetized animals, suggested that this might have been due to a stimulation of tissue metabolism. Craig and Beecher (1943) report that the metabolism of cortex, medulla, and spinal cord slices was markedly diminished by O_2 tensions below 21 per cent of an atmosphere but that only the metabolism of the cortex showed any significant difference for O_2 concentrations ranging between 100 and 21 per cent. It was suggested that perhaps by increasing the O_2 tension of the inspired air the metabolism of the brain in vivo might be increased so as to be significant in relation to the toxic action of high concentrations of O_2.

In experiments on oat seedlings, Albaum, Kaiser and Eichel (1940) found that 50 per cent O_2 increased the rate of O_2 consumption but decreased the rate of growth; pure O_2 however diminished the O_2 consumption, slowed the growth and resulted in a marked reduction in the final length of coleoptile. Stephenson and Whetham (1924) reported that exposure of B. coli to an atmosphere of O_2 increased both the O_2 consumption and the CO_2 output.

The available data concerning the effects of O_2 on nitrogen metabolism are variable and for the most part are unsatisfactory. In determinations on himself, Smith (1870) found an initial decrease in urea excretion for the first four days after beginning the O_2 inhalations, followed by a return toward normal. The experimental method employed, the limited number of experiments performed, and the small volume of O_2 (6 to 8 gals.) respired for only a short period each day render the data of doubtful value. It was claimed, however, that uric acid was diminished by the daily use of O_2 and that the color of urine was changed from dark to light in spite of an increase in specific gravity. Bert (1878) reported that compression of himself to about 2 atmospheres of air, i.e., equivalent to a partial pressure of O_2 of about 40 per cent of an atmosphere, resulted in a slight increase in urea output; in dogs exposed to three atmospheres of air pressure for 9 hours on successive days, he also found a small increase in urea output, but exposure of dogs to air at 8 atmospheres for 6 or 7 hours caused a sharp decrease in urea excretion.

Jaminet (1871) claimed that the urea excretion of caisson workers was increased by their exposure to compressed air. Snell (1896) in observation on himself found that exposure to increased air pressure caused no change in the urea excretion. Terray (1897) concluded from urinary studies that nitrogen metabolism was not altered in breathing O_2 enriched air. Hill and Macleod (1903c) found in their experiments on dogs exposed to air pressures at six to seven atmospheres, i.e., O_2 partial pressures equivalent to about 120 per cent of an atmosphere, that such exposures caused no marked or constant variation in urinary constituents. They considered Bert's findings inaccurate. Adolph (1934) found 100 per cent oxygen increased urine formation in pithed frogs. In summary it may be said that the literature provides no consistent and dependable evidence that breathing hyperoxygenated air or pure O_2 causes any pronounced

alteration in metabolism as manifest by the exchange of respiratory gases and the more numerous reports still favor the interpretation of Seguin and Lavoisier that the respiratory exchange is not a function of the O_2 tension. Yet such a generalization does not dismiss the frequent discrepancies which, while considered inconsequential by some of the authors supporting that generalization may nevertheless be of physiological significance.

Some investigators who have concluded that metabolism is not altered by the administration of hyperoxygenated air at atmospheric pressure have reported, however, that such administration does cause alterations in pulse rate (Benedict and Higgins, 1911). This change in cardiac activity in itself, clearly indicates that breathing increased percentages of O_2 alters the physiological activity of tissue, and in final analysis such alterations must involve changes in fundamental metabolic processes, even though no coincident exchange in gaseous interchange may be readily detected by the techniques usually employed.

A brief consideration of the effects of administration of O_2 in concentrations below that of the normal atmosphere is of interest in this connection: The generalization that a moderate reduction of the O_2 content in the respired air below the normal 20 per cent does not alter metabolism, may account in part for the erroneous interpretation that there is no physiological response to low O_2 administration until the O_2 content of the inspired air falls to about 13 per cent. But the experiments of Bernthal (1938), of von Euler, Liljestrand and Zotterman (1939) clearly demonstrate that even a very small decrease in O_2 content causes distinct alterations in respiratory and circulatory mechanisms. Such alterations constitute further evidence of changes in fundamental metabolic processes. Furthermore the demonstrated effects of O_2 on enzyme preparations (see below) provide ample reason to expect that the administration of O_2 in vivo might result in metabolic alterations.

Breathing. In spite of the general impression and statements in standard textbooks (Starling, 1936; Howell, 1940) to the effect that the inhalation of O_2 enriched air or pure O_2 does not alter breathing, there still crop up dissenters with experimental evidence in support of their claims to the contrary. Certainly a lack of complete unanimity of opinion can be traced back to the very earliest observations on experimental animals and men breathing O_2, hyperoxygenated, or compressed air. Some of these earlier reports were no doubt colored by views of overzealous therapeutists, others by the failure of investigators to recognize the importance of accumulating CO_2 so that many are not admissible as valid evidence of O_2 effects. The legitimacy of admitting data derived from experiments on compressed air as evidence of the effects of increased O_2 alone, may also be questioned; nevertheless even in very recent years compressed air has been employed in experimental studies as a means of providing a desired increase in O_2 concentration, on the assumption that the only variable of physiological significance under compressed air is that of the increased O_2 tension.

Pol and Watelle in a report written in 1847 but not published until 1854, maintained that the rate of breathing was slowed and the thoracic respiratory expansion diminished in men by their exposure to air pressure of about 4 atmos-

pheres—i.e., an equivalent of about 80 per cent of O_2 at atmospheric pressure. Jaminet (1871) and Smith (1886) reported that exposure to compressed air in caissons caused an increased frequency of breathing. Foley (1863) and Bert (1878) observed that pulmonary capacity was increased in compressed air, but that the respiratory movements were diminished in frequency and magnitude.

Kagiyama (1933) found that the frequency of breathing was decreased somewhat by the exposure of his subjects to compressed air at 20 pounds' pressure. The results of Ishikawa's (1939) rabbit experiments also suggest that compressed air causes a decrease in respiratory rate, but his observations were made after decompression. Shilling, Hansen and Hawkins (1935) reported that the vital capacity expiratory force and the ability to hold the breath were all increased in compressed air.

Regnault and Reiset (1849) reported that the respiration of animals was not changed from normal by subjecting them to an atmosphere containing two or three times the concentration of O_2 found in normal air, and Birch (1859) observed that breathing O_2 had no effect on normal men. Terray (1897) reported that O_2 in concentrations up to 87 per cent caused no change in breathing in experimental animals.

The studies of Speck (1879) made on men led him to support the conclusion of Regnault and Reiset. Lukjanow (1884) and Saint-Martin (1884) concluded from experiments on animals and birds that the chemical phenomena of respiration were not altered by breathing hyperoxygenated air, but an examination of the data of each of these latter authors reveals such wide variations as to bring into question the validity of their conclusion.

Loewy (1895), administering O_2 in concentrations up to 49 per cent, found the respiratory rate was diminished but that the minute volume was the same as that when breathing ordinary air.

Benedict and Higgins (1911) concluded from pneumographic studies on human subjects that breathing O_2 caused "no change in respiration either as to character, depth or frequency, as compared with the same factors when breathing ordinary air."

Davies, Brow and Binger (1925) found that in six subjects the respiratory minute volume when breathing pure O_2 was 2.6 per cent higher than when breathing air, but these authors considered this so near the mean deviation that they were unwilling to lay any stress on this increase. Schwab, Fine and Mixter (1936) noted that breathing O_2 (95 per cent) for periods of three hours caused no significant respiratory changes in patients nembutalized for encephalographic studies. Anthony (1940) held that breathing O_2 changed neither the respiratory rate nor the minute volume. Dautrebande and Haldane (1921) reported that breathing O_2 "increases the breathing" but no data were given as to whether this increase involved respiratory rate, depth, or minute volume, and no differentiation was made between those experiments in which pure O_2 was breathed at atmospheric pressure and those in which it was breathed at the increased barometric pressure of about 2.08 atmospheres.

The administration of pure oxygen to anesthetized cats by Wolff and Lennox (1930) caused an increase in the respiratory minute volume. Binger, Faulkner

and Moore (1927) found that more prolonged exposures (6 days) of rabbits and dogs to O_2 in concentrations of 70 per cent resulted in respiratory difficulty characterized by a slow rate, increased depth and exaggerated expiratory effort, but this was apparently due to pulmonary complications for there was an accompanying cyanosis and blood stained froth was present in the mouths of the animals. Comparable effects were observed by Paine, Keys and Lynn (1941) in dogs continuously exposed to O_2 in concentrations of 99 to 100 per cent; forty-eight hours of such exposure caused respiratory distress associated with a decline in the O_2 saturation of the arterial blood and death occurred in 60 hours. Such effects might well be considered as those of deficient rather than excess O_2 supply to the tissues.

Richards and Barach (1934) reported that the resting ventilation of human subjects was slightly increased by breathing hyperoxygenated air (40 to 50 per cent O_2) but the authors questioned whether the increase might not have been due to a small amount of CO_2 which was present in the chamber during the experiments. Behnke et al. (1935) found that the respiratory rate and minute volume of men breathing O_2 remained relatively constant during periods of from eighty minutes to four hours of breathing O_2 except in two cases, one of whom became dyspneic after two hours and the other developed an increased depth and rate of breathing, and symptoms of bronchial irritation in four hours of exposure. Becker-Freyseng and Clamann (1939) became dyspneic within less than two days of continuous exposure to 90 per cent oxygen, but in these experiments, too, there was pronounced pulmonary involvement; no record was made in these experiments or those of Behnke et al. of any possible change which may have occurred in the shift from breathing air to the oxygen.

More recently Shock and Soley (1940a, b) have carried out experiments, using a Siebe-Gorman half mask, on thirty-three university students. They concluded that breathing O_2 over a period of fifteen minutes induces an increased respiratory minute volume. These authors have suggested three explanations for the increase: 1, a diminution in the amount of oxyhemoglobin reduced with a consequent diminution of available base for CO_2 transport as suggested by Gesell (1923) in the case of breathing O_2 at increased barometric pressure; 2, a reduction in the cerebral blood flow so that there is an increased CO_2 in the respiratory centers; 3, an increased sensitivity of the respiratory center to the normal stimulus. The explanation based on a reduced cerebral blood flow does not appear to be compatible with the finding that CO_2 has so powerful a dilating action on pial vessels as to completely mask any constrictor effect which O_2 of itself might exert (Wolff and Lennox, 1930). Moreover, were it simply a matter of vaso-constriction, one would reasonably expect to find a more highly reduced blood than normal in the veins; actually, however, it has been found (Cusick, Benson and Boothby, 1940) that the retinal vessels, which have been used as an index of what occurs in the deeper vessels of the brain, carry more highly oxygenated blood in their venous ends during O_2 administration than they do when air is breathed, in spite of any vasoconstriction which O_2 may induce in such vessels.

The respiratory rate and minute volume of Hough's (1910) healthy human

subjects were decreased by breathing O_2 in concentrations of from 60 to 80 per cent. An examination of the plotted curves presented by Briggs (1920) indicates that breathing oxygen decreased respiratory rate; in seven of ten subjects the rate of breathing was distinctly lower in O_2 than in air, in two there was no difference and in one the rate was lower in air than in O_2. The minute volume, however, showed little or no change. A decrease in ventilation during exposure to hyperoxygenated air was also observed in experimental animals by Campbell (1927), and Hamburger et al. (1932) concluded from their studies on normal men that both ventilation and vital capacity were decreased by breathing hyperoxygenated air.

Marshall and Rosenfeld (1936) say, "It is well known that in a normal animal or man the breathing of pure oxygen has no effect on the rate or the minute volume of respiration," but in their experimental cats anesthetized with phenobarbital sodium and morphine, they found that O_2 breathing caused a decrease in respiratory minute volume and that this decrease became more pronounced with additional doses of barbital or morphine. Under urethane, chlorbutanol, paraldehyde, or alcohol anesthesia, O_2 produced little or no depression in breathing; dogs responded in a manner similar to that of cats. The authors claim that a prolonged apnea produced by O_2 renders the sinoaortic mechanism less sensitive, so that it no longer is stimulated by anoxemia and that under certain conditions of respiratory depression, the administration of O_2 may further depress respiration or even lead to apnea and respiratory failure. In animals given barbiturates or barbiturates plus morphine, the O_2 depression was found to be severe and easily elicited. The administration of 5 or 7 per cent CO_2 to such O_2 depressed animals frequently failed to stimulate respiration.

Binet and Bochet (1938) and Binet, Bochet and Bryskier (1939) reported that breathing O_2 at atmospheric pressure results in a decrease in respiratory rate. Watt, Dumke and Comroe (1943) found in experiments on seven trained unanesthetized dogs that the inhalation of 100 per cent O_2 at atmospheric pressure through a mask for 6 minutes led to a diminution of from 11 to 31 per cent in the respiratory minute volume within the first minute. In four animals the diminution was transient, a return to normal minute volume having been attained within the 6 minutes, but in three the decrease persisted throughout the period of exposure. This diminution in respiratory minute volume was missing after denervation of the chemo-receptors of the carotid and aortic bodies. The authors concluded that some chemo-receptors in the dog must be continually activated by the usual degree of O_2 unsaturation of the arterial blood at sea level, an observation confirmatory to those of Bernthal (1938), Von Euler et al. (1939). In experiments on eleven young human subjects these same authors found that the immediate effect of inhaling 100 per cent O_2 was an increase in respiratory minute volume in thirteen experiments, a decrease in four, and no change in two. The method of O_2 administration and the individual variation among these subjects were not stated, but the authors believed the "findings suggest that tonically active, oxygen-sensitive chemo-receptors are the exception rather than the rule in normal man."

Gesell, Lapides and Levin (1940) found that in administering O_2 in 40 per cent mixtures to dogs the breathing was distinctly less than when breathing 19.7 per cent mixtures and emphasized the nicety of adjustment of reflexogenic breathing to relatively small changes in the O_2 content of the respired air. Keys, Stapp and Violante (1943) found in young healthy men that breathing O_2 (partial pressure of 700 to 715 mm. Hg) at atmospheric pressure through an anesthesia mask (total apparatus dead space 160 cc.) for periods of about 17 minutes caused a small increase in ventilation (average +16 per cent, range −4 per cent to −35 per cent) and a small decrease in the minute volume (average −10 per cent, range −20 per cent to −19 per cent).

The lack of unanimity among the various reports concerning the effects of O_2 administration on breathing may, perhaps, be attributable to various influences which make a comparison of the reported effects and an arrival at a final conclusion difficult, if not impossible. Among such influences might be mentioned (1) differences in the duration of the O_2 administrations, (2) failure to record effects of shifting from normal air to O_2 or vice versa, (3) induction of pulmonary complications with attendant alterations in the O_2 saturation of the arterial blood, (4) the techniques used in the O_2 administration, for example, where masks are used the added dead space may account for some differences, particularly since the response to small amounts of CO_2 in air and in O_2 is not always equal, (5) variations in the degree of O_2 saturation of the arterial blood preceding the O_2 administrations—variations which might be due to a variety of causes such, for example, as depth of anesthesia. Taken as a whole, however, the more reliable evidence indicates that the administration of O_2 does cause changes in breathing and in view of the demonstrated tonic response of chemo-receptors to the normal O_2 unsaturation of the blood, it is perhaps only to be expected that O_2 administration might result in changes in breathing. But at best, these changes are not large and may be readily masked by techniques employed in measurement, nevertheless the data appear to indicate that in animal experiments respiratory minute volume is diminished by breathing O_2; the same may be expected to be true for man but the data, even from more recent investigations, are not unequivocal and for this one may perhaps question to what extent, if any, psychological factors may be responsible.

Circulation. The literature contains numerous reports that increased O_2 either in compressed air or in hyperoxygenated air at atmospheric pressure, causes alterations in pulse frequency. A slowing of the pulse rate as a result of exposure to compressed air has been quite consistently observed (Pol and Watelle, 1854; Foley, 1863; Lange, 1864; Vivenot, 1865; Panum, 1868; Bert, 1878; Heller, Mager and Von Schrötter, 1900; Shilling et al., 1936). However, Loewy (1895) and Hill and Greenwood (1906) found no notable alteration in pulse rate as a result of exposure to compressed air, but the latter authors stated that their observations were not sufficiently extensive to permit any final pronouncement.

Demarquay (1866) and Aron (1901) reported that breathing O_2 tended to increase the pulse rate and Wood and Cerna (1890) concluded from two animal experiments that breathing O_2 was without effect on pulse rate, blood pressure or

circulation in general. Smith (1870a) presented data which showed that of twelve healthy persons breathing O_2 for short periods the pulse rate was decreased in eight and remained unchanged in the other four. "My view," Smith says, "then is, that oxygen acts at the same time upon the heart, to reduce the frequency of its contraction and increase the quantity of blood thrown out at each systole, and upon the blood, to facilitate its flow through the capillaries; that these actions are antagonistic in their effect upon the volume of the pulse and that as one or the other predominates, we shall have the pulse increased or diminished in size, or, if they are exactly apportioned to each other, that there will be no change in volume." Wallian (1889) also concluded that while the effect of breathing O_2 varied to some extent, it almost invariably caused a slowing of the pulse. A similar slowing of cardiac frequency by O_2 was observed by Quinquaud (1884) and Loewy (1895) in animal experiments.

Benedict and Higgins (1911) in their metabolism studies on men found a very distinct decrease in pulse rate as a result of breathing high concentrations of O_2 (40 to 90 per cent) at atmospheric pressures. Convincingly consistent confirmatory evidence that the breathing of O_2 or hyperoxygenated air at atmospheric pressure causes a decrease in pulse rate in man is found in the data and conclusions of numerous later investigators (Parkinson, 1912; Dautrebande and Haldane, 1921; Katz et al., 1932; Behnke et al., 1934; Anthony, 1940; Anthony and Kümmel, 1939; Davis, 1941; Keys, Stapp and Violante, 1943). Schwab, Fine and Mixter (1936) reported that the heart rate of patients nembutalized for encephalographic studies was decreased by breathing 95 per cent O_2 but that this bradycardia persists only for about one-half to one hour after the beginning of the exposure, then disappears. Becker-Freyseng and Clamann (1939) found that exposure to 90 per cent O_2 caused a decrease in pulse frequency during the first 15 hours but with continued exposure the pulse frequency increased somewhat, due no doubt to pulmonary complications.

Steinhaus, Jenkins and Lunn (1930) experimenting with unanesthetized dogs which had been used for daily metabolism tests for over a period of twenty months found, however, that the administration of O_2 from a Sanborn-Benedict apparatus caused no significant change in pulse rate from that obtaining when breathing ordinary air. Binger, Faulkner and Moore (1927) reported that the administration of O_2 in concentrations of about seventy per cent at atmospheric pressure to dogs gave rise to distinct cardiac arrhythmia with extra systoles.

Reports concerning the effects of O_2 on blood pressure are less consistent than those on pulse rate. Vivenot (1865) held that the magnitude of the radial pulse was decreased in compressed air but that the systolic pressure was increased. Bert (1878) recorded an increase in the pulse pressure as well as in both the maximum and minimum blood pressures of animals exposed to air compressed to several atmospheres; the respiratory oscillations in pressure were also increased. These changes Bert attributed to the mechanical effects of the increased air pressure rather than to the effects of the increased tension of O_2, since he found that the administration of O_2 in concentrations of about 35 per cent at atmospheric pressure caused no such changes. Jacobson and Lazarus (1877) and Zadek

(1880) reported that the blood pressure increased in compressed air. Smith (1886) claimed that the volume of the pulse was always diminished in compressed air. Loewy (1895) observed that the blood pressure remained constant or showed a very moderate increase and that the circulation of the blood was not changed from normal in animals under such conditions.

Bennett and Smith (1934) reported that exposure of rats to compressed air caused pulmonary hypertension, an affect which was attributed to the increased O_2 tension. The recent work of Shilling et al. (1936) indicates that both systolic and pulse pressures are decreased in compressed air and that the cardiac output, as calculated from the formula of Furst and Soetbeer (1906), is decreased on an average of about one liter per minute.

Wolff and Lennox (1930), in an experimental study on anesthetized cats, found that high concentrations of O_2 at atmospheric pressure lowered both the blood and spinal fluid pressures; the authors pointed out, however, that the O_2 satura-

TABLE 1

96 to 99 per cent O_2 inhalation (subject lying on a cot one atmosphere)

SUBJECT	DURATION OF EXPOSURES TO O_2	PULSE RATE		BLOOD PRESSURE		
		Start	Finish	Start	Finish	
1	80–240 min.	80 Air	59.8 O_2	121/77 Air	118/84 O_2	Av. of 5 readings
2	120–240 min.	84.3 Air	68 O_2	121/76 Air	119/79 O_2	Av. of 6 readings
3	120–235 min.	69 Air	58.5 O_2	124/74 Air	121/86 O_2	Av. of 4 readings
4	100–240 min.	86.4 Air	66 O_2	127/80 Air	120/83 O_2	Av. of 5 readings
9	125 min.	60 Air	66 O_2	120/66 Air	136/66 O_2	1 reading, subject dyspneic
10	240 min.	68 O_2	60 O_2	128/68 O_2	108/80	1 reading, bronchial irritation, respiratory reaction

tion was slightly subnormal before the O_2 inhalations were begun. The administration of O_2 to anesthetized cats for two minutes during constant artificial respiration resulted in a slight rise in blood pressure (Schmidt, 1934). Davis (1941) however found that breathing O_2 caused no significant changes in the blood pressure of anesthetized dogs.

Behnke et al. (1934) in summarizing their data from experiments on human subjects lying on a cot breathing O_2 in concentrations of from 96 to 99 per cent at atmospheric pressure, state that in all of the O_2 exposures, the blood pressure was constant except in two cases. The authors make no specific reference to the alterations induced by the shift from air to O_2 but an examination of their tabulated data from six subjects reveals that the average systolic blood pressure was decreased and that the diastolic pressure was increased by breathing O_2 in all except one subject; in the exception, who had become dyspneic, the systolic pressure was increased by breathing O_2 and the diastolic pressure remained the same as when breathing air. A compilation of averages made from the data of Behnke

et al. is shown in table 1 above. Such data would seem to support a conclusion that systolic pressure is decreased, diastolic pressure slightly but distinctly increased with a consequent drop in pulse pressure, and that the pulse rate is definitely diminished, by breathing O_2.

Keys, Stapp and Violante (1943) reported that in young men breathing almost pure O_2 at atmospheric pressure caused a slight but consistent rise (4 mm. Hg) in diastolic blood pressure and a tendency to an increased systolic pressure; the pulse pressure was somewhat decreased. There was a slight decrease in cardiac "work" and "effort" but no significant change was observed in either cardiac size (roentgenkymograph) or in cardiac efficiency.

Katz et al. (1932) noted in their study of O_2 therapy for cardiac cases that neither the arterial nor venous blood pressure, of their control subjects (human) was altered significantly by breathing hyperoxygenated air but the T wave of the E.K.G. was lengthened; the change was not explainable on the basis of any possible relief of arterial anoxemia. Schwab, Fine and Mixter (1936) observed no significant change in blood pressure of nembutalized patients as a result of their exposure to 95 per cent O_2 for three hours. Anthony (1940) reported that breathing O_2 caused a decrease in stroke volume of the heart and changes in the E.K.G. Richards and Barach (1934) found that the cardiac output of normal men was not changed by their residence in hyperoxygenated air (45 per cent O_2) at atmospheric pressure.

A perusal of the evidence leaves little doubt but that breathing O_2 or hyperoxygenated air at atmospheric pressure causes a predominant slowing of the heart: the reports concerning blood pressure changes are not unequivocal, but pulse pressure is seemingly diminished.

Vascular Changes. The early reports to the effect that breathing hyperoxygenated air at atmospheric pressure or compressed air caused peripheral vascular changes were based for the most part upon observation of changes in skin colour of individuals during their exposure to compressed air and in some cases even after their decompression to normal pressure. Such changes were not infrequently attributed to the supposed direct mechanical effect of the pressure itself.

The experiments of Poiseuille (1835) in which he demonstrated by direct observation that the peripheral capillaries of frogs, tadpoles and salamanders were not altered by the animals' exposure to compressed air should have dismissed the notion that either the pressure itself or the attendant increase in O_2 tension, caused any distinct constriction of the peripheral vessels. But in spite of this work, the contention of Bert (1878), and the observation of Hunter (1887) that no constriction occurred in the fundic vessels of men on their exposure to compressed air, the idea that in compressed air the increased pressure *per se* caused a peripheral vasoconstriction was held and argued by numerous investigators, typified by Vivenot (1865) and Smith (1870, 1886) even to the early 1900s.

Hill and Macleod (1902), unaware of Poiseuille's experiments and feeling the need of further experimental evidence on the question of a peripheral vascular constriction, exposed frogs to high pressures of air by a technique similar to that of Poiseuille and found no alteration in capillary circulation even at pressures as

high as 70 atmospheres. Thus the findings of Poiseuille were abundantly confirmed and the interpretation that increased pressure *per se* or increased O_2 tension in the compressed air, was shown to be untenable.

L. Smith (1899) had suggested that the lung changes he observed in animals which had been exposed to high O_2 pressures might represent an attempt on the part of the organism to protect the tissues against excessively high O_2 tensions. Following this suggestion of a protective reaction it was only natural that attempts would be made to look for other protective mechanisms; and what more convenient or purposive mechanism could there possibly be imagined than one which closed off the O_2 supply to the tissues by constricting the blood vessels?

Dautrebande and Haldane (1921) performed experiments which, as they said, "were undertaken for the purpose of seeing whether any evidence could be obtained that the tissues of the nervous system are defended against the influence of oxygen by diminution of the circulation through them." The conclusions drawn from their experiments have been accepted so frequently as substantial evidence of a vasoconstriction induced by O_2 that the argument of the authors is presented here.

"If the circulation is diminished when oxygen is breathed," they said, "it is evident that the pressure of CO_2 in the tissue must rise; and in the respiratory centre this rise of CO_2 pressure will, other things being equal, imply rise of hydrogen ion concentration and consequent increase in breathing and fall of alveolar CO_2-pressure. A very slight fall in alveolar CO_2-pressure will, however, suffice to compensate for the rise in CO_2-pressure in the tissues in consequence of a sufficient slowing down of the circulation to reduce the oxygen-pressure of the venous blood to normal. Complete compensation could not, however, be expected, since otherwise there would be no stimulus left to account for the slowing down of circulation."

"The problem which we set ourselves to investigate, therefore, was whether there is any fall in alveolar CO_2-pressure when oxygen at increased partial pressure is breathed. We also watched the pulse carefully, as any diminution in pulse-rate would serve as an index of slowing of the circulation." These investigators did find a drop in the alveolar CO_2 partial pressure of about 1.5 mm. Hg and a slowing of the pulse when O_2 was breathed at normal barometric pressure, and remarked, "The experiments therefore confirm the theory (which is in itself probable from many considerations into which we need not enter here) that the excess of free O_2 in the arterial blood causes slowing of the circulation." The validity of this argument and the supposed evidence of vasoconstriction are obviously open to very serious question, especially since there was also an increase in breathing which of itself would lower alveolar CO_2 tension.

Retzlaff (1913) concluded from plethysmographic studies that O_2 caused a vasoconstriction in the lungs. Faulkner and Binger (1927) reported that the capillaries in frogs were not noticeably affected by the administration of O_2 in concentrations as high as 95 per cent.

Tinel (1927) observed a dilatation in the exposed superficial vessels of the brain of cats on the cessation of O_2 inhalation. Rebreathing from a bag of O_2

did not produce vasoconstriction; on the contrary a vasodilatation (probably due to accumulated CO_2) was observed. From these findings Tinel suggested that O_2 caused vasoconstriction and that the cerebral circulation may be regulated by the O_2 content of the blood. Campbell and Hill (1931) suggested that Tinel's claim might be put to the test by an observation of the retinal vessels; Duke-Elder (1931) making such an examination found no change from normal in the vessel calibre when his subjects breathed O_2 for periods of five minutes.

Wolff and Lennox (1930) in studies on exposed pial vessels of cats observed that an increase in the O_2 tension caused a slight vasoconstriction, and the addition of small amounts of CO_2 to the respired gas resulted in pronounced dilatation which masked the distinctly lesser tendency for constriction by O_2. The authors were reluctant to accept their results as indicative of similar cerebral circulatory influence of O_2 on man for two reasons: 1, because their experimental animals were under amytal anesthesia; 2, because the vessels in the pial covering, they thought, may act differently than the vessels in the brain substance. They further cautiously pointed out that the changes they observed may have been related to the sub-normal arterial O_2 saturation (75 per cent) obtaining before the O_2 inhalation (due, perhaps, to the anesthesia) and a rise to 95 per cent saturation on the inhalation of the O_2. They maintained that it does not necessarily follow that a similar increase in arterial O_2 above normal would give a comparable vascular change.

In studies relating blood flow and inhalation of various O_2-CO_2 mixtures by human subjects, Lennox and Gibbs (1932) found that when breathing pure O_2 the O_2 content of the arterial blood increased by 1.2 volumes per cent. The changes in blood flow, they found, were comparatively slight and inconsistent. "The results," they say, "therefore are indecisive, there being evidence of a slight decrease in the speed of blood flow through the brain and more consistent evidence of an increased flow through the leg." The same authors found that an increased CO_2 tension of the arterial blood caused an increased flow through the brain and a decrease through the leg. The reciprocal allotment of blood flow through the brain and through the peripheral tissue during O_2 inhalation would appear then to be just the reverse of that induced by CO_2 administration; excess O_2 seems to favor, though to small degree, an increase of blood flow to the periphery while excess CO_2 favors a shift of flow to the brain.

This observation on the reciprocal adjustment to CO_2 confirms the findings of Gesell and Bronk (1926) that the administration of CO_2 caused an increased blood flow through the carotid artery and to the brain. Bronk and Gesell (1927) and Bernthal, Bronk, Cordero and Gesell (1928) not only showed that both low O_2 and CO_2 increased the volume flow of blood through the carotid artery, but that there was a parallel increase in the blood flow through the vertebral artery, thus demonstrating that carotid blood flow is a safe index of the blood flow through the brain. The breathing of pure O_2 at atmospheric pressure, or O_2 in 50 per cent mixtures, caused a decrease in the carotid and femoral volume flow of blood.

Kroetz (1930) deduced from experiments on normal human subjects that

breathing O_2 at increased concentrations caused a large increase in the volume flow of blood and an increase in the O_2 tension of the tissues.

The view that O_2 causes a vasoconstriction in the brain finds some support, however, in the experiments of Schmidt (1934) on the regulation of the circulation in the hypothalamus of the cat. He observed that the administration of O_2 occasionally gave a slight vasoconstriction as indicated by a thermo-junction thrust into that tissue. Dumke and Schmidt (1943) measured the cerebral blood flow through the basilar and internal carotid arteries in nembutalized Macacque monkeys and found "there was a distinct hint of a constrictor action" when breathing oxygen (100 per cent), but this effect was never at all marked; a dilating effect of CO_2 (10 per cent) was consistently observed. When CO_2 is administered along with increased O_2 tensions any vasoconstrictive influence which O_2 may exert on pial or retinal vessels is nullified by the dilating action of the CO_2; the result is an increased blood flow to the brain (Wolff and Lennox, 1930; Cobb and Fremont-Smith, 1931; Cusick et al., 1940).

Cusick, Benson and Boothby (1940) found that breathing pure O_2 at atmospheric pressure for 30 minutes, decreased the calibre of both arterioles and veins in human retinae by from 10.5 to 37.7 per cent; usually this change was more marked in the veins. It was also observed that in spite of any constriction which occurred when breathing O_2, the venous blood was much redder than when breathing air. Similarly Cobb and Fremont-Smith (1931) observed in men that the colour of the retinal veins became arterial when CO_2–O_2 was breathed.

Rosenthal (1939) reported that in fifteen human subjects the inhalation of O_2 caused a narrowing of physiological angioscotomas; after the withdrawal of the O_2 there occurred a widening of the scotomas to areas in excess of that preceding the O_2 administration. The pattern of the narrowing induced by O_2 inhalation followed that of the retinal vessels which suggested the effect was of peripheral rather than of central action of the O_2; the retinal synapse was proposed as the probable site of this influence. Cusick et al. (1940) interpret Rosenthal's findings as due to the involvement of an O_2 vasoconstriction.

An evaluation of the evidence concerning the influence of O_2 on vessel calibre supports the conclusion that O_2 at atmospheric pressure does cause a slight vasoconstriction in the C.N.S. and retinae. But the fact that the venous blood is not normally reduced when breathing O_2 indicates that if this vasoconstriction is a reaction on the part of the organism to protect its tissues against an excessively high arterial O_2 tension, it is grossly inadequate as a protective mechanism. The finding that a relatively small increase in CO_2 completely masks any vasoconstrictive influence of O_2 is important, not only in the interpretation of vasomotor responses to breathing O_2 at atmospheric pressure, but also and especially in the interpretation of the effects of O_2 at pressures above one atmosphere. In any case a localized vasoconstriction cannot be regarded as an infallible index of a generalized vasoconstriction,—a point well emphasized by Wiggers (1942) in connection with his studies on shock.

Blood. In recent years a renewed interest in the blood changes induced by breathing O_2 rich mixtures has become manifest. This interest has been for the

most part concerned with the changes in cell counts, cell size, and hemoglobin. Heller, Mager and von Schrötter (1900) observed no significant change in the R.B.C.'s of caisson workers as a result of exposure to the increased air pressure, but Bornstein (1911) found that exposure of a dog to air pressure of about two atmospheres from October to the following April caused a decrease in the R.B.C. count and a drop in hemoglobin from 100 to 85 per cent; these and similar changes found in growing dogs and a monkey, but not in pigeons, were attributed to an increase in the blood volume. Ishikawa (1939) likewise reported that exposure of dogs to compressed air (80.85 or 130 lbs.) caused a decrease in hemoglobin content of the blood.

Karsner (1916) after having made careful studies on twelve control animals in which he found considerable variation in the R.B.C. counts (between 8,460,000 and 5,512,000 per cm.) stated that prolonged exposure to high concentrations of O_2 (80 per cent to 90 per cent) at atmospheric pressure, appeared to produce no material changes in the erythrocyte count that were not observed in control animals living for similar periods under the same general conditions. The variation in the per cent of reticulated R.B.C.'s of the control animals was such (2 to 25 per cent) that no very definite conclusion could be made concerning the action of O_2 on this type of cell. Likewise, the resistance of the R.B.C.'s to hypotonic solutions, and the hemoglobin percentage as determined by the Talquist scale, showed no distinct changes.

In four out of five of Karsner's experimental animals there was a consistent and appreciable leucocytosis as a result of the O_2 exposure (the fifth animal was not acceptable because of an abnormally high count before exposure). This increase in leucocytes was apparently unrelated to the occurrence of pneumonia observed in the O_2 exposed animals; Karsner believed it was "probably to be explained only as accidental variations so frequently seen in the rabbit." There was a pronounced phagocytosis of the R.B.C.'s in the lymph nodes of the O_2 exposed animals and this was thought to be associated with the passive congestion found in other organs. The bone marrow of ten animals exposed to O_2 showed no distinct departure from the picture seen in the controls. The clotting time was likewise unaffected by the O_2 exposures.

Full and von Friedrich (1923) subjected healthy men, diabetics, and hemiplegic patients to O_2 at pressures of $+10$ to $+8$ cm. of H_2O by means of a gas mask and found there was a significant decrease in hemoglobin content of the blood. They concluded that this change was caused by a movement of tissue fluid, low in albumin, sugar, and NaCl, into the blood stream. Izumiyama (1928) in somewhat similar experiments found that breathing O_2 at both atmospheric and at slightly increased pressures ($+8$ to $+20$ cm. H_2O) caused a decrease in both hemoglobin content (10 to 20 per cent) and in the R.B.C. count. However, since the mechanical effects of an unequalized positive pressure may cause reflex and direct circulatory changes, it is questionable whether the results of these experiments may be safely interpreted simply as O_2 effects.

Barcroft, Hunt and Dufton (1920) studying the treatment of chronic gas poisoning by residence in a chamber containing O_2 in 50 per cent concentrations,

found that when the R.B.C. count before the treatment was greater than five million the treatment reduced the count, but when it was less than five million subsequent residence in the O_2 chamber did not alter it.

Campbell (1927a b) concluded that exposures to hyperoxygenated air at atmospheric pressure (O_2 content as high as 200 per cent above normal), for 3 or 4 weeks caused a decrease in both hemoglobin percentage and in the R.B.C. count in rabbits, rats, mice, "cavies", and monkeys (cats were not so affected; but the color index increased). These results suggested that Bornstein's earlier finding of a decreased R.B.C. count in compressed air was due to the increased O_2 tension, but Campbell disagreed with Bornstein's interpretation that such change was caused by a hemodilution, because of the lack of parallelism between changes in hemoglobin and R.B.C. count. Although the color index increased in Campbell's animals during the exposure to the increased O_2 to a point resembling that observed in pernicious anemia, neither the size nor the type of R.B.C. was altered.

In the experiment in which the reticulated R.B.C.'s were examined, Campbell found 8 per 1000 at the end of a four weeks' exposure to the increased O_2 tension, whereas ten days after return to normal air they had increased to 80 per 1000. This suggested that the high O_2 concentration decreased the formation of R.B.C.'s, but in view of the fact that this represents data from only one experiment, that apparently no pre-exposure estimation was made, and that very wide variations in reticulated cells occur even under ordinary conditions (Karsner, 1916), perhaps the results are less significant than they might at first appear. The changes in the white cells were not sufficiently consistent to be significant, but the differential counts showed the lymphocytes were appreciably increased by the O_2 exposure.

Achard, Binet and LeBlanc (1927) found an increase in both the R.B.C. and leucocyte counts in their experimental animals (guinea pigs and rabbits) after 48 hours of exposure to 80 per cent O_2 at atmospheric pressure with a partial return to normal at the end of 120 hours of exposure. It was later reported (Binet and Bochet, 1938; Binet, Bochet and Bryskier, 1939) that breathing hyperoxygenated air caused an initial decrease followed by an increase in the R.B.C. count to values as high as 150 per cent above normal. It was also noted (Binet, Bochet and Guiraud, 1939) that while 70 per cent O_2 mixture caused decrease in the R.B.C. count of guinea pigs and rabbits within the first few hours of exposure, it might still be subnormal after several days. Very similar initial results were observed in guinea pigs with 40 per cent O_2 mixtures and in men breathing 60 per cent O_2 from oxygen tents. The results reported by these investigators suggest that the lack of unanimity of opinion among various investigators as to the effects of increased O_2 concentrations on the R.B.C. counts, may perhaps be explained by differences in the time at which the counts were made and in the concentrations of the O_2 employed.

Anthony and Bechthold (1939) noted that in men even the first few minutes of breathing O_2 caused a drop in the hemoglobin content of the blood and a decrease in the R.B.C. count. These changes were only temporary, however, for within fifteen minutes recovery had begun and after fifty minutes the original values

had been regained. The decrease in hemoglobin and R.B.C. count was attributed to an increased blood volume resulting from a shift in tissue fluid (Anthony, 1940). Paine, Keys and Lynn (1941) reported a marked increase in the hemoglobin (associated with a decline in O_2 saturation of the arterial blood) of dogs exposed to 90 per cent O_2 for several days. Davis (1941) found a slight but constant increase in both the hemoglobin content and in the R.B.C.'s as a result of administering O_2 (1000 cc. per min.) by nasal catheter to anesthetized dogs, but the W.B.C.'s were reported to be definitely decreased by as much as 10 to 30 per cent of their initial value. Behnke et al. (1934) found an increased leucocyte count in three men after four hours of breathing O_2 at one atmosphere pressure. Becker-Freyseng and Clamann (1939) observed a very distinct increase in the leucocytes (from 6,200 to 12,700) but only a very slight increase in R.B.C.'s in themselves as a result of their exposure to O_2 in concentrations of about 90 per cent.

The size of the blood cells has also been found by various observers to be altered by breathing increased concentrations of O_2. Mannasein (1872) reported that the diameter of the R.B.C.'s was increased by breathing O_2. Gunther (1928) observed that breathing O_2 caused a decrease in R.B.C. diameter from 7.14 μ to 6.72 μ. Similarly Hitzenberger and Molenaar (1934) reported that in healthy persons the breathing of O_2 for twenty minutes caused a decrease in both the diameter (from 7.3 μ to 7.1 μ) and the volume of the R.B.C.'s as well as a decrease in serum albumin and an increase in blood volume. The dilution of the blood was attributed to tissue fluids flowing into the vessels from plasma depots and a release of water from the R.B.Cs. The authors think that prolonged changes in the O_2 tension in the air breathed—even that associated with the usual changes in barometer reading——may cause a distinct effect on the blood and its constituents.

Schmidt-Lange and Podloucky (1937) likewise found that in mice, guinea pigs, and rabbits the diameter of the R.B.C.'s was decreased by breathing O_2 and thought this was due to a disturbance of the O_2-CO_2 relation and the acid base equilibrium of the body. All of the ten healthy persons studied by Anthony and Bechthold (1939) showed an average decrease in R.B.C. diameter of 2.1 per cent as a result of breathing O_2. This was attributed to an increased alkali binding ability of the oxyhemoglobin. Taken as a whole the reports on cell size indicate that breathing O_2 or hyperoxygenated air caused a decrease in R.B.C. diameter.

The reports of chemical changes occurring in the blood as a result of exposure to increased concentrations of O_2 have not been very extensive. That there is an increase in the amount of O_2 in solution has, of course, long been recognized, even before the time of Bert. Quinquaud (1884) found that breathing pure O_2 increased the O_2 content of the arterial blood 2.2 volumes per cent. Hough (1910) explained the changes in breathing which he observed in O_2 at concentrations of 60 to 80 per cent as due to an increase of 1.2 volumes per cent of O_2 dissolved in the blood of his subjects. Hill (1912) gives the O_2 solubility of the blood at body temperature as 2.4 volumes per cent. This would mean, assuming complete

equilibrium in the lungs, that the O_2 carriage by the blood to the tissues would be increased by more than 10 per cent if the alveoli were filled with O_2. Lennox and Gibbs (1932) found that the O_2 content of arterial blood in man was increased 1.2 volumes per cent by breathing pure O_2, but that the CO_2 content was not appreciably altered. Analyses made by Binger, Faulkner and Moore (1927) showed that in dogs after several days' exposure to hyperoxygenated air (70 per cent O_2), the arterial blood was only 40 per cent saturated. Such a finding is particularly significant in relation to O_2 therapy; it indicates that while breathing O_2 may initially increase the O_2 content of the blood, its continuous administration to a point where lung damage is induced, may actually result in subnormal O_2 content of the blood.

Ishikawa (1939) reported that exposure of dogs to air pressures of from 60 to 130 pounds caused a decrease in the blood lactic acid and an increase in blood sugar. Davis (1941) found that O_2 administration to dogs caused no significant change in blood sugar, chlorides or N.P.N., but that there was a decrease in CO_2 combining power of the blood which persisted for as long as twenty minutes after cessation of the O_2 administration. Mention has already been made of reports on changes in blood urea and CO_2 (see section on metabolism).

Influence of O_2 on Enzymes. Investigations carried out in recent years provide ample evidence that increased concentration of O_2 at atmospheric pressure inhibits enzyme activity. That this should be so is perhaps not so surprising in view of the inhibitory effects of increased O_2 tensions in some inorganic reactions. Brooks (1942) points out that O_2 is an inhibitor of many inorganic thermal and photochemical reactions and his own experimental data suggested that in the oxidation of hemoglobin, O_2 acts both as a reactant and inhibitor as it does in the case of irradiated quinine (Weigert, 1912).

Laqueur (1912) reported that the rate of proteolysis in liver tissue was slowed by O_2. McCance (1924), studying autolysis, found that urea formation was inhibited by O_2. Voegtlin and Maver (1932) and Maver, Johnson and Voegtlin (1933) showed that a decrease in O_2 tension accelerated proteolysis. Lee and Chen (1938) reported similar results from experiments on acid glycerol extract from sheep liver and that this inactivation of proteolytic enzymes was only partially reversible. Libbrecht and Massart (1934) also found proteolytic enzymes were inhibited by O_2. The experiments of Bailey et al. (1942) likewise show an inhibitory action of O_2 on proteolytic enzymes. Albaum, Donnelly and Korkes (1942) working with oat seedlings found suggestive evidence that increased O_2 tension interferes with proteolysis. Rondoni and Pozzi (1933) however reported the rate of proteolysis in liver extract was not altered by O_2.

Marks and Fox (1933) and Marks (1935a, b) found that catalase from some species of marine plants and 19 marine animals were inactivated either directly or indirectly by O_2 and enzyme assays of Albaum et al. (1942) carried out an oat seedlings thirty hours after the grain had been soaked in oxygenated solution showed that such oxygenation decreased catalase activity.

Albaum et al. (1942) also found that oxygenation decreased the endogenous dehydrogenase activity of oat seedlings, and Shapiro and Wertheimer (1943) re-

ported that the O_2 in room air readily inhibited the activity of fatty acid dehydrogenase in mixtures with coenzyme and substrate. Formic dehydrogenase of B. coli has also been found (Gale, 1943) to be inactivated by increased O_2 tension. Lehmann (1935) reported that the activity of succino-dehydrogenase had its optimum O_2 tension at from 44 to 56 mm. Hg; at higher tensions it was very distinctly lowered. This toxic effect of increased O_2 tension was said to be irreversible and the critical pH value for this effect lay in the neighborhood of 7.4. In studies on Acetobacter peroxydans, Weiland and Pistor (1938) found lactic acid dehydrogenation was inhibited by O_2.

In experiments on red blood cells (human) and tissue slices, Jowett and Quastel (1933a, b) found that glyoxalase activity was diminished by O_2, that this inhibitory effect increased as the exposure was continued, and that it was a reversible process. The authors indicated that this effect of O_2 is probably due to a partial oxidation of glutathione which results in a decreased co-enzyme concentration and thus of enzyme activity.

Hellerman, Perkins and Clark (1933) and Hellerman (1937) also report that O_2 has an inhibitory influence on many enzyme systems and emphasize the importance of the presence of heavy metal ions in some of these inhibitory reactions. It was found that several hours' aeration of highly purified, crystalline urease reduced the activity by only about 10 per cent, but in the presence of cupric ions the ureolytic activity was completely abolished by aeration for only one-half hour and irreversibly destroyed by aeration for 3.5 hours. These results were interpreted to indicate that the "poisoning" effects of cupric ions were not due to the ions themselves but rather to their ability to accelerate the oxygenation of urease. This influence of the ions of heavy metals such as iron, and especially copper, was also pointed out to be operative in the case of cysteine which, in highly purified form, was reported to be but slowly attacked by O_2 but when in the presence of ions of iron or copper it, as was true also for other thiol compounds, was rapidly oxidized.

Pathology. The first suggestion that breathing O_2 caused pathological effects seems to have come from the observations of Priestley. Lavoisier (1783) was aware of these observations and having, as he said, occasion to repeat some of Priestley's experiments chose guinea pigs for the purpose. Autopsies were performed on these animals which had died in "vital air" and he found that in every instance death appeared to have been caused by "une fievre ardent" and a "maladie inflammatoire." "The flesh was a *very red* colour; the heart livid, and turgid with blood, especially the right auricle and ventricle; the lungs were very flaccid, but *very red*, even externally"; they were also engorged with blood.

Beddoes, one of the earliest advocates of the therapeutic use of O_2, recognized that the injudicious use of O_2 might cause pulmonary damage. He says, "It is not then defect but excess of Oxygene that is pernicious here. The heart and arteries pulsate more quickly and forcibly; the eyes grow red and seem to protrude; the heat of the body is said to considerably increase (a), sweat to break out over the whole body and fatal mortification of the lungs to come on. These appearances denote violent inflammation. The production of inflammation is fully

established by dissection" (Beddoes and Watt, 1796). An experiment was performed on a large kitten which was kept for seventeen hours in an atmosphere of 80 per cent O_2. At autopsy it was found that the lungs were a florid red color. The edge of one lobe "was marked with livid spots (as in mortification). The pleura was likewise evidently inflamed"; the lungs of the control kitten were "pale."

The first report of any extended experiments on the action of O_2 in successive exposure appears to be that of Dumas (1866) who, thinking O_2 might have some "baleful" action on some types of phthisis, tested his theory on a dog. A healthy animal was placed in a large chamber in which the air had been replaced by O_2 and which was fitted with inlet and outlet tube for maintaining a constant purity of the gas. The animal was kept in this atmosphere for a period of six hours, at the end of which time its respiration appeared to become "more precipitate, more rapid"; the animal was then moved to ordinary air. This same procedure was repeated twice a day for 28 days, at which time, because of manifest respiratory difficulty, the periods of O_2 exposure were shortened but continued for 15 days longer. At that time the dog's breathing had become "sonorous, sibilant and laborious," his weight had fallen, and he became emaciated. The animal was killed, and its lungs examined; the right side of the thorax was found filled with "acrid serum and coagulated blood; the bronchial tubes were filled with fluid; the pleura was tightly adherent to the lungs especially at the bases which were adherent to the adjacent parts. The membrane was red, tumefied and as if affected by inflammation. The lungs, red and seamed with little rents, had become considerably solidified as occurs in the case of organs which have been for some time inflamed." In the vicinity of the bronchial tubes there was found a suppurating abscess. Dumas says, "The anatomical inspection of these organs, therefore, did not permit one to doubt that O_2 had induced an irritating action upon the lungs and that from it had resulted all the ordinary symptoms of phthisis." Demarquay (1866), another ardent O_2 therapeutist, recognized a danger in the use of O_2 and maintained that particularly in the presence of a tendency "to an inflammatory state this gas may give rise to accidents."

Although the data from these early experiments can be accepted only with some degree of reservation due to the small number of experimental animals employed and the question of adequate controls, they do find support in later and more carefully controlled investigations.

Moir (1895) reported that mules which had been continuously exposed for several months to compressed air at about 30 pounds' pressure in the Hudson Tunnel showed no adverse effects. This was taken as evidence that O_2 in concentrations equivalent to 60 per cent of an atmosphere is innocuous. Smith (1899) found pronounced pulmonary pathology in mice, birds, rats, guinea pigs and pigeons which had been exposed to O_2 at atmospheric pressure. The alveoli were filled with a "granular" exudate; no leucocytes were present. The condition resembled the "earliest stages of croupous pneumonia." In addition to pulmonary "inflammation," congestion, and consolidation, there was also congestion of other organs, particularly the liver, spleen and kidneys. The pa-

thology was essentially the same in both mammals and birds. The higher the O_2 tension the earlier was the onset of the inflammatory reaction, but O_2 at tensions equivalent to 40 per cent of an atmosphere was without effect and failed to produce pneumonia in mice which had been exposed to it for as long as eight days. In O_2 concentrations of about 80 per cent, however, some mice died after only four days of exposure. Smith pointed out that the autopsies of individuals dying of caisson sickness had sufficient features in common with O_2 poisoning to suggest that the increased O_2 tension in compressed air may contribute to the pathology of caisson sickness.

Hill and Macleod (1903c) observed that O_2 at atmospheric pressure did not cause any symptoms of pneumonia in mice in a 6 hour exposure. Air at a pressure of 5 atmospheres for periods up to as long as 24 hours likewise caused no symptoms of pneumonia. It was believed that such a duration was too short to induce any distinct lung pathology. But at air pressures of 7 atmospheres there occurred gasping and death and at autopsy extensive pathology resembling that described by Smith (1899) was found in the lungs. The authors denied, however, that the increased O_2 tension in the air pressures commonly employed at that time was a contributory factor in the occurrence of caisson sickness as Smith had claimed.

Schmeidehausen (1909), using mice, rabbits and guinea pigs in experiments in which some of the animals were exposed to pure O_2 at atmospheric pressure in a chamber and others breathed O_2 through a tracheal cannula, found pathological changes in the lungs characterized by hyperemia, edema, atelectasis and inflammatory processes; but no *true* pneumonia occurred in exposures of less than 69 hours. David (1912) demonstrated changes essentially similar to those of Schmeidehausen. Schmidt and David (1911, 1912) emphasized the danger in the prolonged use of O_2 in chloroform anesthesia and claimed that even in concentrations as low as 40 to 60 per cent, O_2 by itself induces inflammatory changes in the lungs if the exposure be prolonged to 70 hours.

Bornstein and Stroink (1912) found that continuous breathing of O_2 in concentrations as low as 60 per cent for several months produced anemia in a dog and monkey and that at somewhat higher percentages, desquamation, edema and inflammation with some hemorrhage occurred. Brüning (1912), however, claimed the changes described by these two authors were really caused by the dryness of the gas rather than by the O_2 itself, to which charge Bornstein (1912) replied in defense of the evidence of Bornstein and Stroink.

Adams (1912), experimenting with guinea pigs, found that breathing O_2 in concentrations of about 80 per cent caused death in from three to four days. Post mortem examination showed the lungs to be markedly congested, all the lobes were distended; the heart was engorged as in asphyxial death; exudate was present in the alveoli and the epithelium showed desquamation; bacterial smears and cultures made from the cut lung were negative. Death was attributed to an acute "lobar or catarrhal pneumonia." It was concluded that O_2 in concentrations below 70 per cent can be inhaled for prolonged periods without giving any symptoms of pathology, but in higher concentrations its use is attended with serious risk of causing an irritative pneumonia and death.

Karsner (1916), emphasizing the need of further studies on the possible pathology induced by breathing atmospheres rich in O_2, carried out investigations dealing with the effects of O_2 in 80 to 96 per cent mixtures at atmospheric pressure. Great caution was observed in the matter of controls since autopsies had frequently revealed the presence of significant pathology in supposedly normal, non-symptomatic laboratory animals—especially rabbits.

Among the changes induced by increased concentrations of O_2 Karsner found dilatation of either the right or both sides of the heart in animals which had succumbed to, or survived, 2 to 5 days of exposure to the increased O_2; cloudy swelling became practically uniform in the longer exposures. The aorta showed no notable change. The liver was passively congested, and this, it was thought, might or might not have been associated with hemosiderin pigmentation, but it was not prominent until after 72 hours of exposure when it was associated with intercellular edema; the stomach and intestines were also congested.

In the kidneys too the most prominent change was one of congestion; cloudy swelling appeared to be more evident in the kidneys of high O_2 animals than in the controls, but Karsner questioned if the difference was great enough to be of significance. Albuminuria appeared in two of the O_2 exposed rabbits; six positive cases of interstitial nephritis which occurred were explained as having probably arisen from the superimposition of passive congestion on kidneys already diseased, but diseased so that under ordinary conditions albuminuria did not exist. The adrenals and spleen showed no significant alteration other than that of congestion. Lymph nodes appeared to indicate a more marked phagocytosis of R.B.C.'s associated with the passive congestion. Bone marrow from ten exposed animals showed no distinct difference from that of the controls and the blood was not thought to be significantly altered.

Karsner, like Hill and Macleod (1903c), was impressed by the wide individual variation in susceptibility to the effects of O_2 poisoning. He suggested that the susceptibility to the deleterious effects of O_2 might be accentuated by living through the diseases which caused the non-experimental lesions—a point of considerable interest, especially to those O_2 therapeutists who have maintained that a damaged lung is less susceptible to any injurious effect of O_2 than a normal lung. Karsner's finding of fibrin in the inflammatory reactions of the lungs is contrary to that of Smith (1899), but both of these investigators reported that the leucocytes were not significantly altered. The passive congestion in the lungs and all abdominal viscera and which was accompanied by "secondary changes such as cloudy swelling of the parenchymatous organs and phagocytosis of erythrocytes by endothelial cells of the mesenteric lymph nodes" was attributed by Karsner to the failure of the heart, either as a whole or its right side. It was concluded that "atmospheres containing 80 to 96 per cent oxygen under normal barometric pressure produce in 24 hours, or more commonly 48 hours, congestion, edema, epithelial degeneration and desquamation, fibrin formation, and finally a pneumonia, probably of irritative origin and to be described as a fibrinous bronchopneumonia." Further work by Karsner and Ash (1916) confirmed these findings and also showed that while 53 per cent O_2 caused no change in rabbit lungs in exposures of about 3.5 days, 67 per cent induced slight evidence of pneumonia but

no true inflammatory reaction and 75 per cent caused early pneumonia in exposures carried out over longer periods.

Barach (1926) found that normal rabbits exposed for from one to four months to O_2 in concentrations up to 60 per cent at atmospheric pressure were unaffected in their general appearance, behavior, growth or weight. Tissues examined after one and two months of exposure showed no gross or microscopic pathology. The exposure to O_2 at 70 per cent, however, caused pulmonary changes characterized by an edema. These experiments led to the conclusion that 60 per cent is the upper limit of concentration at which O_2 might be used safely for extended periods in therapy.

Binger, Faulkner and Moore (1927) were of the opinion that the numerous reports of pathological effects induced by breathing O_2 enriched atmospheres might have been due to inadequate removal of CO_2, undue temperature, humidity and the movement of air in the small quarters in which so many of the experiments had been carried out. They considered it desirable, therefore, to investigate the problem under conditions where these various factors and the respiratory infections, which they, like Karsner, found so prone to occur in caged animals, could be ruled out. The first abnormal sign which they noted in their experimental dogs subjected to an atmosphere of 70 per cent O_2 was a refusal of food on the third day and a subsequent loss of weight; vomiting occurred on the fifth day and drowsiness on the sixth. Labored breathing, becoming progressively more severe, was first noticed on the sixth day and was characterized by its slow rate, increased depth and expiratory effort. No significant variations in body temperature were evident. On the eighth day the dogs were removed—in one there was marked cyanosis and cardiac arrhythmia diagnosed by electrocardiogram as due to extra systoles; blood-stained froth was pouring from the mouth. Analysis of arterial blood showed only a 40 per cent O_2 saturation. The second dog showed no anoxemia or respiratory distress and its arterial blood was 94.6 per cent saturated. The third dog had respiratory disturbances similar to, but less severe, than that observed in the first; its arterial blood showed a 93.7 per cent O_2 saturation.

At autopsy the lungs of the most severely affected dog were found collapsed and mottled, "beefy red—bright in some areas and dull red in others"; no normal tissue was found and the trachea was full of blood-tinged froth. Microscopic sections showed a general destructive process of a non-infectious character involving all parts of both lungs, characterized by: (1) capillary engorgement with some hemorrhage; (2) presence of interstitial and intra-alveolar serum; (3) hypertrophy and desquamation of alveolar cells; and (4) interstitial and intra-alveolar infiltration of mononuclear cells. No micro-organisms were found in any of the sections examined. The lungs of the second dog were normal except for an apparent capillary engorgement. The lungs of the third dog were collapsed; there were a few small hemorrhagic areas and capillary engorgement. The gross appearance of all the other viscera was essentially normal. Blood from the hearts in all three dogs was sterile and lung puncture material showed no bacterial growth on blood agar.

In the rabbits—placed in separate cages with these three dogs—the first symptom of significance was marked respiratory dilatation of the alae nasi on about the sixth day of exposure. This respiratory disturbance progressed to one of distress, a gasping inspiration with involvement of accessory muscles of respiration. Cyanosis was present in all three rabbits by the seventh day and two died. The third was taken from the chamber at this time, but had a convulsive seizure and died a few minutes after exposure to normal air. The autopsies revealed pathology very similar to that found in the dogs. Guinea pigs survived O_2 for four days and the lungs at that time had the gross appearance of liver and sank in fixing fluid. Two mice survived the O_2 for six days; lung pathology was similar to that of the guinea pigs. Two mice kept as controls in a similar chamber remained normal.

These investigators questioned whether their findings might not have been caused by some impurity in the O_2 due to the method of its preparation (Burrows, 1917) and therefore ran a series of tests on mice. They found that O_2 prepared by air reduction, by the electrolytic process, and that purified by bubbling through olive oil to remove any traces of ozone, all produced the same effects, thus ruling out the possibility that the pathology might have been caused by some impurities in the O_2. The authors agreed with the view that O_2 in concentrations greater than 60 per cent of an atmosphere causes a rapid deterioration in the mammalian organism, and in concentrations over 70 per cent is poisonous to dogs, rabbits, guinea pigs and mice. The poisonous effects manifest themselves in drowsiness, anorexia, loss of weight, increasing dyspnea, cyanosis and death from oxygen want because of a destructive lesion of the lung. This lung alteration was not characteristic of an infectious process and was interpreted as a possible protective reaction which, progressing too far, causes death. "The organism, in its unsuccessful effort to achieve a new equilibrium, is kept alive by the very environmental condition which ultimately destroys it."

Faulkner and Binger (1927) found, however, that frogs were not noticeably affected by O_2 in concentrations as high as 95 per cent. Turtles likewise appeared to be unaffected at their usual body temperature, but if the body temperature was raised to that of mammals, the general response to O_2 and pulmonary pathology was essentially the same as that of mammals; young turtles were more resistant to this change than the older ones. In looking for an explanation of these effects the authors suggested that perhaps a reaction takes place between O_2 and pulmonary tissue, the temperature coefficient of which is such that it occurs at body temperature of mammals but not at room temperature; or that a chemical irritant is produced which acts on the lung or that the metabolic rate is raised, thereby increasing the toxicity of O_2.

Achard, Binet and LeBlanc (1927), experimenting on guinea pigs and rabbits, also found that 80 per cent O_2 caused distinct pulmonary pathology and death. Guinea pigs survived three to five days and rabbits about five to six days. In addition to the pulmonary congestion, desquamation and consolidation described by other investigators, the alveolar walls were found to be infiltrated with leucocytes and eosinophils. Hubbs (1930), experimenting with ozone and hydrogen

dioxide, concluded that the lethal action of these substances on aquatic animals must be caused by "nascent oxygen."

The evidence which had accumulated up to this time would seem amply to warrant convicting O_2 as a dangerous agent, but Smith, Heim, Thomson and Drinker (1932) were unconvinced and suspected that the evils of excess O_2 had been exaggerated. Their skepticism was not unlike that voiced by Binger, Faulkner and Moore (1927): "No previous work on the toxicity of increased oxygen tension in the respired air," said Smith et al., "has been conducted under conditions in which all the other factors were constantly and perfectly controlled, and most of the investigations on this subject have been based upon data obtained from observing a limited number of animals." They decided to gather new data. The animals chosen for their investigation were albino rats from Wistar stock. These were exposed to compressed air at 3040 mm. Hg pressure (an O_2 partial pressure of 635 mm. Hg, i.e., an O_2 equivalent of 83.6 per cent at normal barometric pressure). Since the work was intended as a very careful study on O_2 effects it is perhaps unfortunate that the possible complicating influence of increased N_2 concentration and physical factors of increased air pressure were not ruled out by the use of O_2 mixtures at atmospheric pressure.

The pathology found by Smith et al. in rats exposed to compressed air and attributed by them solely to the increased partial pressure of O_2, was very similar to that observed by other investigators in animals exposed to increased concentration of O_2 at atmospheric pressure. In adult rats (over 5 months old) there was dilatation of the heart, congestion of the viscera and some tubular damage in the kidneys manifested by areas of degeneration and the presence of mitotic figures in the tubular epithelium. The lungs were dark beefy red and very intensely edematous. There was pleural effusion, and considerable emphysema was present in the alveolar ducts. The capillaries of alveolar walls were engorged with R.B.Cs. and the arteries and veins were surrounded by large zones of perivascular edema with varying degrees of cellular infiltration. The trachea, bronchi and bronchioles were not affected.

Young rats under forty days of age showed no evidence of this O_2 damage except for an early perivascular edema, dilatation of the lymphatics, and slight cellular infiltration; in rats 100 days old these changes were more pronounced and in addition there was some desquamation, hyperplasia and hypertrophy of alveolar cells. Numerous mitotic figures were found in the alveolar walls of rats which had apparently become adapted to the increased pressure and the hyperplasia persisted for months after the rats were returned to normal air pressure. It was this increased pulmonary "cellularity," believed to be induced in adult rats by O_2 at increased tension, but normally present in young rats, which the authors claimed was responsible for an increased resistance and adaptation to O_2 poisoning; this adaptive change, it was said, prevented the development of O_2 poisoning on re-exposure (see section on acclimatization). These authors maintained that the higher mortality in older non-adapted rats was to be explained by the loss of the young lung characteristics.

Boycott and Oakley (1932) concluded that the cause of death in rats exposed

to increased percentages of O_2 at atmospheric pressure was massive pleural effusion. In O_2 concentrations of 95 to 99 per cent about one-half of their experimental animals (rats) died, but no symptoms appeared in less than two or three days. On the fourth day all the animals developed progressive dyspnea; in the next two days some became worse and died while others recovered. Dyspneic rats brought into normal air died within one-half hour. The thorax was found to be full of clear liquid and the lungs completely collapsed. Capillaries were congested, fluid was found in alveoli; many monocytes but no polymorphonuclear leucocytes were found in the lung. The rest of the body (except for a general congestion attributable to circulatory failure) appeared normal. These authors suggested that the high concentration of O_2 irritates the endothelium of the pulmonary capillaries so that it lets through everything in the blood plasma except the cells. Another change noted by these investigators was that white rats kept in O_2 in concentrations of 65 per cent and up had a patchy yellowing of the fur.

Pflesser (1937) reported that mice breathing O_2 in concentrations of 86 to 92 per cent at atmospheric pressure died in about 35 to 45 hours; cats exposed to O_2 in concentrations of 93 to 97 per cent died in 70 to 86 hours. The cause of death was failure of the heart and circulation and edema of the lung with pleural exudate. Orzechowski and Holste (1938) concluded from experimental studies, that the minimum lethal O_2 concentration for the rat was determined in large part by the total air pressure—an observation which points to the possible danger of making quantitative inferences concerning the effects of O_2 percentage from compressed air data. Clamann and Becker-Freyseng (1939) conclude from animal experiments that inhalation of O_2 rich atmospheres containing more than 60 per cent O_2 at atmospheric pressure leads to the death of the animal in hours or in a few days and that the cause of death is primarily lung pathology due to the action of O_2 and not to any contaminations in the gas.

Armstrong (1938) states that breathing pure O_2 has caused fever within six hours in both man and experimental animals. His animals developed pneumonia in from 12 to 36 hours of exposure to O_2 at atmospheric pressure and died in an average of 72 to 90 hours of exposure. The pathology was essentially that as described by earlier investigators—irritation of the respiratory tract with congestion, edema, pneumonia and death. Experiments were also performed in pure O_2 at decreased barometric pressures. In O_2 at pressures equivalent to from 0 to 5000 feet altitudes (i.e., from 760 to 625 mm. Hg) the animals (rabbits) appeared normal for 12 to 24 hours, there then occurred a slowing and deepening of respiration. Evidence of air hunger became progressively more pronounced and death occurred at zero altitude pressure in an average of 84 hours, and at 5000 feet altitude pressure in an average of 156 hours. The lungs at autopsy were liver-like in appearance and consolidated; the pleural cavity contained a small amount of colorless fluid; there was edema with leucocytes present and capillary engorgement; the large blood vessels were dilated and contained much serum. At 10,000 feet altitude pressure (513 mm. Hg) a few of the animals developed symptoms of air hunger on about the sixth day and died between the eighth and tenth days;

the animals exposed to from 20,000 to 30,000 feet altitude pressures showed no abnormal behavior and no pathology; at 50,000 feet altitude pressure the animals succumbed in about three minutes and these at autopsy showed death occurred from suffocation. Having made these observations, Armstrong concluded, "From this it is evident that pure oxygen should not be administered below an atmospheric pressure of 456 mm. Hg (13,465 feet)." This tension of O_2, it will be noted, is just 60 per cent of one atmosphere, a concentration which has been considered for some time as the upper limit of safety in prolonged therapeutic administrations.

Binet and Bochet (1938) and Binet, Bochet and Bryskier (1939) observed that guinea pigs exposed to O_2 in concentrations of 96 to 98 per cent at first tolerate the O_2 without much change, but there is a tendency to lethargy and a torporous state, alternating with periods of activity; secondarily, the torpor is accentuated, anorexia is common and the animal curls up in a ball; respiration becomes dyspneic and the animal soon dies of asphyxia. The lungs show desquamation, congestion, thickened alveolar walls, leucocytic and eosinophilic infiltration, and there is generalized congestion. In continuous administrations of O_2 the toxic action appears in a relatively short time, but with intermittent inhalation the survival is much prolonged. The authors conclude that continued breathing of O_2 has a definite toxic action which is manifest by respiratory, biochemical, hematologic, and histologic reactions and eventually by death. They too, maintain that a concentration of 60 per cent at atmospheric pressure is the upper limit for safe administration of O_2 therapeutically.

The findings of Rehbock et al. (1940) emphasize further the lung pathology arising from exposure to increased concentrations of O_2 (80 to 85 per cent) at atmospheric pressure. Among their findings in animals dead on the 4th and 7th days of exposure were "generalized intra-alveolar and perivascular exudate; in animals dead on the 14th and 16th days of exposure, severe suppurative bronchitis with varying degrees of bronchiectasis . . . large areas of bronchopneumonia characterized by a dense intra-alveolar exudate of polymorphonuclear leucocytes." They further observed, "The arterioles and smallest arteries showed no definite changes except for slight thickening of the walls of an occasional vessel or occasional foci of hyaline change. There was a condensation of new adult connective tissue around the adventitia of the large arteries. . . . Three animals exposed for twenty-eight days and dead on the thirtieth and forty-first days, showed extensive broncho-pneumonia with abscesses, bronchiectasis, and emphysema. The arteries and arterioles showed only the slight changes seen in previous animals." Such data suggest that death from prolonged exposure to O_2 may be caused not only by acute edematous changes and characteristic "pneumonia" which result in asphyxia, but possibly also by exacerbation of pathologic processes—particularly those of suppurative character—previously resident in the lung. On the other hand the experiments of Marcheaux (1943) on rats indicate that previous damage induced in lungs by vagotomy does not augment the susceptibility of those lungs to the adverse effects of O_2 tension.

Bennett and Smith (1934) described progressive sclerotic changes, thickening,

narrowing and hyalinization in the pulmonary arterioles and arteries of rats, commencing as early as the third day of exposure to compressed air at 3040 mm. Hg (O_2 equivalent 83.6 per cent at atmospheric pressure). The changes appeared to these authors to be similar to the renal arterial lesions seen in patients dying of malignant hypertension. Dilatation of the right ventricle found in their experimental animals was attributed to the pulmonary vascular lesions. These changes were considered as having been caused by the increased O_2 tension.

Rehbock, Oldt and Dixon (1940), however, found no indication of any sclerotic changes in animals exposed to O_2 at from 80 to 85 per cent for periods of from 4 to 28 days. The perivascular fibrosis described by Bennett and Smith (1934) and Smith, Bennett, Heim, Thomson and Drinker (1932) in the compressed air experiments was found, but no medial or intimal changes were observed. A very definite right ventricular hypertrophy was demonstrated in animals on which autopsies were made 7 to 41 days after the beginning of the O_2 exposures; a less significant right ventricular hypertrophy was present in the animals 7 to 14 months after the exposure. The examination of animals after survival periods of from 7 to 15 months likewise showed no noteworthy changes in the arteries or arterioles except for a possible increase in the collagenous tissue of the adventitia in larger vessels.

Paine, Lynn and Keys (1941) have contributed still further confirmation of the damaging effects on breathing O_2 in high concentrations. In a series of experiments on 49 dogs they found that definite pulmonary changes resulted from breathing O_2 in concentrations of 95 to 100 per cent at atmospheric pressure for periods as short as two hours. One dog died after only six hours of exposure and at autopsy showed the typical pulmonary pathology, but the average duration of survival in concentrations of from 95 to 100 per cent was 39 hours. These experiments demonstrate again the wide individual variation in susceptibility to the action of O_2. Oxygen concentrations of from 75 to 90 per cent produced pathologic changes similar to those seen in the 95 to 100 per cent concentrations, but the time of onset was more delayed. Occasional interruption of O_2 administration delayed the onset of toxic symptoms and prolonged the period of survival. The symptomatology and pathologic findings reported by Paine et al. are in agreement with those of earlier investigators but they also included cyanosis of the muscles and abdominal viscera, gaseous distention of the stomach and in some cases there was a marked atrophy of the hepatic parenchyma in the central part of the lobules said to be comparable to that seen in right heart failure.

Definite pathologic lesions were found even in exposed animals which had shown no symptoms of the damaging action of O_2—an observation of interest in relation to the use of high concentrations of O_2 in therapy. The authors say, "It is not impossible that most or all of the pathologic changes, which we have observed, might be explained by an hypothesis of deranged vascular physiology." While the number of animals used in this investigation contribute in large measure to the value of the experimental results, it is perhaps to be regretted that no mention has been made of controls which Karsner (1916) found were so very important in pathological studies of O_2 poisoning in laboratory animals. The

CO_2 content of the respired air in these experiments varied between 0.2 and 2.0 per cent of an atmosphere.

Kaunitz (1942) reported that subjecting mice to pure O_2 at atmospheric pressure for two or three days results in myocardial lesions consisting of "marked degeneration and fragmentation of the muscle fibres, some of which show granulation and loss of striation. Capillary dilatation presumably due to congestive heart failure is also to be noted." It was maintained that while at first the O_2 reaches the alveoli with ease, the bronchi later go into spasm, become filled with mucus and so obstruct the air passages that the resulting decrease in intra-alveolar pressure causes the alveoli to collapse; the experimental evidence of this sequence of events is not presented. The myocardial lesions were said to be caused by the anoxemia consequent upon the pulmonary lesions. The number of animals examined and the condition of the controls, if any, were not stated. Pichotka (1941) and Liebegott (1941) also reported cardiac pathology including leucocytic and lymphocytic infiltration, and necrosis of muscle fibers, and attributed this to hypoxemia arising from the lung damage induced by the O_2. Rehbock et al. (1940) found ventricular hypertrophy in dogs exposed to 80 to 85 per cent O_2.

Marechaux (1943) described pathological changes in rat lungs as a result of exposure to O_2 in concentrations of 81.5 per cent; in addition to the more usual changes previously described there was edema of the blood vessel walls (gefaszwandödem) and border striations (randstreifen) in the alveolar walls which the author suggested were comparable to the "Quellungs Nekrosen der Alveolarwände" previously described by Liebegott (1941), Clamann, Becker-Freyseng and Leibegott (1942). Pichotka (1941) had also noted this "Quellungs Nekrosen" in addition to other pathology and pointed out that the lung picture was similar to that of phosgene poisoning; pneumococci type X were also observed. Behnke and Willmon (1941) describe what they believe to be a new clinical entity of delayed pain, congestion and hemorrhage in the middle ear following O_2 inhalation during high altitude pressure changes; these effects which develop chiefly during sleep have been attributed by the authors to a reduction in the middle ear pressure resulting from the absorption of the contained O_2.

In summary then the more outstanding pathology as revealed by tissue examination would include the following: inflammation, congestion, edema, atelectasis, fibrin formation and consolidation in the lungs; pneumonia of various types, bronchitis with bronchiectasis; hypertrophy, hyperplasia, desquamation and degenerative changes in alveolar cells; sclerotic changes with narrowing, thickening and hyalinization of pulmonary arterioles; dilatation of the right or both sides of the heart; cardiac hypertrophy and cloudy swelling; congestion of abdominal viscera with cloudy swelling in the kidneys; splenic contraction and testicular degeneration. The long accumulation of experimental data leaves little question but that continuous exposure to O_2 in concentrations above 60 to 70 per cent at atmospheric pressure for from 12 to 14 hours or even less, results in pathological changes particularly in the lung, and that if exposure is further prolonged these changes frequently prove fatal. The onset of the noxious effect on

man may be more delayed than in other animals, but there is good reason to believe that the human animal is similarly affected. (See section on noxious effects of O_2 at atmospheric pressure and O_2 therapy.)

Acclimatization and Tolerance. Campbell (1927) observed a decrease in breathing of as much as 30 per cent in animals exposed to an O_2 rich atmosphere. It was claimed that this change in ventilation together with an observed decrease in both the hemoglobin per cent and R.B.C. count, constituted a mechanism by which the organism attempted to acclimatize itself to the high O_2 tensions. It was further suggested that vascular changes and a shift in the dissociation curve of hemoglobin might also contribute to this acclimatization whereby an excess uptake of O_2 by the tissues might be prevented. These mechanisms, however, quite evidently did not succeed in holding the O_2 level of the tissues at their normal values, for both the O_2 and the CO_2 tensions of the tissues were found to be increased as a result of breathing the hyperoxygenated air. When the animals were returned to normal air there was hyperpnea and a distinct drop in the tissue CO_2 tension—a reaction which was interpreted to mean that now the O_2 tension of normal air was insufficient normally to sustain the O_2 acclimatized animal. In any case this post-exposure hyperpnea indicates that during the exposure to the hyperoxygenated air there had been some adjustment to the O_2 enriched air which was incompletely or slowly reversible, and the fact that the O_2 concentration employed was distinctly less than that which it is generally agreed causes lung changes, would localize this acclimatization to some tissue beyond the lung membranes. Campbell suggests that the hemoglobin-forming organs are regulated by the O_2 tension, but Karsner's (1916) examination of blood and tissues, including that of bone marrow, revealed no evidence in support of that suggestion.

In their entirety, the reports on red cell and hemoglobin content of the blood hardly justify a conclusion that there is any one predominant adaptive response in the hematopoietic system to breathing O_2 or hyperoxygenated air; on the other hand the consistent finding of a decrease in red cell size and a common, though not invariable, leucocytosis, is highly suggestive of the operation of some more or less universal adaptive mechanisms which affect the cellular characteristics of blood.

Smith (1899) suggested that the pulmonary pathology induced by exposure to O_2 might act as a protective barrier against the entrance of too much O_2 into the blood. Such changes have been referred to by some authors as an "acclimatization,"—perhaps a misuse of the term, since those changes commonly prove fatal during the animal's sojourn in O_2 or after its return to normal air.

Barach (1926) in an attempt to determine whether the lungs might be capable of acquiring some degree of acclimatization or immunity to the injurious effects of O_2 in high concentrations, subjected rabbits to a gradually increasing O_2 concentration from 21 per cent to 85 per cent, or to a maintained high O_2 percentage just below toxic concentrations. No evidence of acclimatization was obtained; subsequent exposure to O_2 in concentrations of 80 to 85 per cent invariably produced a serous pneumonia.

Boycott and Oakley (1932) observed that if rats, dyspneic from an exposure to

O_2 at increased concentrations were brought into ordinary air, many of them died within half an hour, "Their pulmonary condition is evidently such that they can survive only in high concentrations of oxygen." The survivors of O_2 exposure experiments continued to live normally in 95 per cent O_2 for some time though they were still liable to die on coming into air, but after about a month or six weeks they began to deteriorate. "They become peeky, deteriorate in morale and do not clean themselves, lose their appetites, waste and die, and in this sequence of events there is much individual variation. They do not become anaemic and at post mortem there is no obvious cause of death, though in one or two instances there has been a small pleural effusion." Controls living for longer times under exactly the same conditions in 50 to 55 per cent O_2 remained well. The authors refer to this post-exposure deterioration as "chronic O_2 poisoning."

That changes take place in an animal as a result of exposure to O_2 enriched air which are not readily reversible when returned to normal air is shown again in the experiments of Binger, Faulkner and Moore (1927); a rabbit exposed to 70 per cent O_2 at atmospheric pressure for three days had a convulsive seizure and died when it was taken from the O_2 chamber and replaced in room air.

Smith, Heim, Thomson and Drinker (1932) and Smith, Bennett, Heim, Thomson and Drinker (1932) maintain that acclimatization or adaptation takes place in the lungs of rats on prolonged exposures to increased O_2 concentrations. By the fourth day of exposure to compressed air at 3040 mm. Hg (an O_2 equivalent of 83.6 per cent of one atmosphere) they found pronounced symptoms of O_2 poisoning, anorexia, loss of weight, respiratory embarrassment, hyperpnea and cyanosis, in rats over three months of age; 13 per cent succumbed. The surviving rats showed improvement by the sixth day although there was still anorexia and weight loss, but the animals of this group sacrificed for autopsy, showed that the pathological changes found in the third and fourth day rats, were missing. Young rats (under three months of age) showed a depression in normal growth rate, but appeared to be unaffected otherwise.

After 72 days of exposure, decompression to atmospheric pressure was carried out; 28 per cent of those still alive at the end of the 72 day exposure died during, or within twenty-four hours after, their return to normal air pressure and at autopsy all of these showed severe lung damage, particularly broncho-pneumonia. The survivors of decompression showed no signs of O_2 poisoning when, after a 40 day interval in normal air, they were re-exposed to compressed air; and only 2 in a litter of 8 born during the second exposure died, whereas during the first exposure all of 9 litters born, died. The absence of any fatalities on decompression from this second exposure to compressed air is in contrast with the high mortality (28 per cent) on decompression from the first exposure. It may be noteworthy, however, that the first exposure was seven times longer than the second. The authors interpreted their results as evidence that during the first exposure there had developed an increased resistance to the toxic effects of O_2 which was of the nature of a permanent adaptive change.

The essential feature of this adaptive reaction was described as a pulmonary change, characterized by hypertrophic and hyperplastic alterations in the pul-

monic capillary bed and in the properties of the alveolar cells. The thickening and increased "cellularity" of the alveolar walls was similar to that found in normal non-exposed rats under 3 months of age. It was thought that this peculiar morphology, considered as having been developed in the adult rats by O_2 exposure, but normally present in young rats, was the cause of the greater O_2 resistance observed in the adult adapted, and in the young unadapted rats. If this interpretation be correct, one may perhaps with reason ask why all of nine litters born during the first exposure to compressed air succumbed; unless, of course, the peculiarly resistant morphology is absent in very young lungs.

This evidence presented by Smith et al. (1932) does unquestionably suggest there is some pulmonary adaptation to increased concentrations of O_2. But the high mortality met with in the process of its development (13 per cent early in exposure and an additional 28 per cent on return to normal air) indicates that this adaptive response is either absent in many individuals or that there is a very wide variation in its effectiveness; some of the data may perhaps be also interpreted as a reflection of a selective process. The recognized wide individual variation in susceptibility to O_2 poisoning, the pathological findings in so-called normal animals (Karsner, 1916) and the fact that practically all those rats which succumbed showed broncho-pneumonia, might well imply that a selective process was operative and that possibly the toxic action of O_2, superimposed upon a pre-existing sub-symptomatic pathology was the cause of death. Since, however these experiments were carried out in compressed air, rather than in O_2 or hyperoxygenated air at atmospheric pressure, some degree of reservation may be called for in assuming that the results are attributable solely to the increased O_2 tension.

Nelson and Gowen (1930) reported that the incidence of "spontaneous" pneumonia in rats increases with age up to one year, at which time about 75 per cent of the animals are affected; in young animals, less than three or four months old, the occurrence of pneumonia was relatively infrequent. This again suggests the possibility that the greater resistance to O_2 poisoning observed by Smith et al. in rats under three months of age might have been due to an absence of pre-exposure lung pathology in their young animals. The surprisingly extensive involvement of the lungs necessary to induce any symptoms of pulmonary pathology in rats (Griffith and Farris, 1942) emphasizes the impressively wide margin of safety provided in the lungs and the danger, where autopsies are not performed, of assuming that an absence of signs or symptoms is indicative of either an immunity to the effects of increased O_2 tension or an absence of pulmonary damage induced by O_2.

Rats advanced in pregnancy were reported (Smith et al., 1932) to be more susceptible to O_2 poisoning in compressed air than non-pregnant, owing, it was thought, to encroachment upon the thoracic cavity by the gravid uterus, but Ozorio de Almeida (1934) found that pregnant rats were no more susceptible to the toxic effects of O_2 at high barometric pressure than the non-pregnant.

Evidence has already been cited that exposure to O_2 at increased tension depresses metabolism. Such a reaction in itself might conceivably be interpreted as a protective or adaptive response and suggests that an organism's basal

metabolic rate may be intimately concerned with its susceptibility to the adverse effects of O_2 at increased tensions. Evidence that this is so is found in several reports. Faulkner and Binger (1927) observed that raising the temperature of turtles increased their susceptibility to the adverse effects of prolonged breathing of O_2 enriched air at atmospheric pressure, and Campbell (1937) noted a similar effect of increased temperature in mammals.

Clamann and Becker-Freyseng (1939) maintain there is an inverse relationship between the size of an animal and its susceptibility to the deleterious action of O_2; and this, it is claimed, is related to the lower metabolism of large animals in terms of their body surface. Binet, Bochet and Bryskier (1939), however, found that in O_2 concentrations of 90 per cent at atmospheric pressure, mice survived longer (140–150 hrs.) than guinea pigs (60–70 hrs.). Ham and Hill (1906) and Hill (1912c) likewise reported that small animals are not more susceptible than large. Thompson (1889) found the monkey was affected before the pigeon, and the dog before the guinea pig. Smith (1899) found no relationship between the size of the animal and its susceptibility to O_2 poisoning. Nor does the data of Soulie (1939) concerning the species' susceptibility show any distinct relationship between size and survival in O_2 exposures; mice survived as long as rats.

It has been widely accepted that basal metabolism decreases with the approach of maturity, in man and other animals (Magnus-Levy and E. Falk, 1899; Aub and DuBois, 1917; Kise and Ochi, 1934; Matson and Hitchcock, 1934; Lewis, 1938; Davis and Hastings, 1934; Benedict and Macleod, 1929; Kibler and Brody, 1942; and others). If then there is a direct parallelism between the susceptibility of an animal to the adverse effects of O_2 and its basal metabolism, young immature animals should be more affected by O_2 than older full grown animals but this is contrary to the findings of Smith et al. (1932) in rats and those of Thompson (1889) and Binet, Bochet and Bryskier (1939) in pigeons. Paine et al. (1941) observed however that young pups were just as susceptible as full grown dogs. The factors of growth and immaturity no doubt introduce some peculiar influence which further complicates the relationship between body size, metabolism and susceptibility to the toxic action of O_2.

Interestingly enough Benedict and Macleod (1929) claimed that the generally accepted interpretation that the metabolism of smaller animals is greater than that of large animals is erroneous; they found that in terms of surface area the metabolism of the white rat is actually less than that of man. But Dubois (1929) maintained that little animals have a higher metabolism and respiration per unit weight than large animals so that their tissues should become more rapidly saturated with the respired gas. Since there is some disagreement among authorities concerning the relationship between body size, inherent metabolism and the best method of expressing that relationship, especially where different classes and species are concerned (Krogh, 1916; Benedict and Macleod, 1929) it would appear wise to exercise caution in the interpretation of differences in susceptibility to O_2, on the basis of reported differences in basal metabolism. If small animals are more susceptible than large, perhaps a greater rapidity of blood circulation is causally involved in addition to possible differences in metabolism.

Soulie (1939) reported that when animals are exposed in alternating periods of 24 hours' duration to normal air and to O_2 in high concentrations (90 to 100 per cent at atmospheric pressure) there occur no indications of any physiologic disturbance or O_2 poisoning; but if after about six weeks of such treatment the animals are continuously exposed to the increased O_2 concentration they react and die just as untreated animals do. If, however, continuous inhalation of high concentrations of O_2 at atmospheric pressure be carried to the point of appearance of pulmonary symptoms and this is repeated intermittently, the resistance of the rat to O_2 poisoning can be augmented. It was also maintained that a similar augmentation of resistance to increased O_2 per cent can be accomplished by inhalations of sublethal concentrations of disphogene but guinea pigs do not develop tolerance by these methods as well as rabbits.

The report of Rehbock, Oldt and Dixon (1940) is of interest in relation to the question of adaptation. These investigators found that rats, dead on the fourth day of exposure to O_2 in concentrations of 80 to 85 per cent at atmospheric pressure, showed the characteristic pulmonary pathology ("fibrinous pneumonia") arising from such treatment; those animals dead on the seventh day of exposure showed the same but less severe damage. In animals dead on or after the fourteenth day of exposure these changes were absent although there was other pathology present. The diminishing severity of the "fibrinous pneumonia" with prolongation of exposure may be variously interpreted; it may represent a progressive development of pulmonary resistance or acclimatization to the toxic action of O_2, or again it may indicate simply a selective action of the toxicity for the more susceptible individuals.

The best explanation for those respiratory difficulties so frequently experienced by animals on their return to normal air after a prolonged exposure to O_2 or hyperoxygenated air at atmospheric pressure and which with some stretch in the meaning of the term might be considered a manifestation of "acclimatization," would appear to lie in the pulmonary pathology which such exposure is known to produce. Certainly the changes in hemoglobin and red cell content of the blood mentioned above could hardly account for the post exposure respiratory difficulties. There is, however, another possible contributor less obvious than that of lung damage which may deserve some consideration, namely, an alteration in fundamental enzymatic processes in the tissues. The impressive evidence that increased tensions of O_2 inhibit and evenly irreversibly damage some of the respiratory enzymes provides reasonable basis for the speculation that such enzymatic changes may contribute not only to acclimatization, but also to the post-exposure reactions. The report of Boycott and Oakley (1932) cited above that animals deteriorated and died of "chronic O_2 poisoning" without showing at autopsy any obvious cause of death is of interest in this connection.

The reports that patients to whom O_2 or hyperoxgenated air has been administered therapeutically, occasionally have difficulty in readjusting to ordinary air, constitute further argument that some adaptive changes of slow reversibility, similar to that occurring in experimental animals, and quite aside from pulmonary alterations, are evoked by the O_2 treatment. Armstrong (1939) observed that

animals which had shown symptoms of pneumonia as a result of exposure to pure O_2 at normal or reduced barometric pressures died almost immediately when removed to normal air. This was interpreted as due to an alteration in the diffusion of O_2 consequent upon the pulmonary inflammation induced by the O_2 and led Armstrong to suggest that pneumonia patients receiving O_2 therapeutically should never have the O_2 supply stopped suddenly.

Additional evidence that the return to breathing normal air after exposure to O_2 at one atmosphere causes some disturbance is found in the report of Behnke et al., (1934) that while a subject felt well during the inhalation of O_2 he experienced substernal discomfort and coughed during the first half hour after his return to normal air. It has also been occasionally observed that after long periods of O_2 administration in anesthesia, a sudden removal of the mask is followed by profound circulatory disturbances, particularly an extreme drop in blood pressure. These effects imply a lag in reversibility of adaptive changes other than pulmonary. Waters (1942) questions whether such disturbance might not represent the inability of the organism to readjust immediately to the normal biochemistry of blood and tissues which have become accustomed to high tensions of O_2 and CO_2.

NOXIOUS EFFECTS OF O_2 AND THERAPY. Some of the early advocates of the use of O_2 for therapeutic purposes (Priestley, 1775; Beddoes and Watt, 1796; Beddoes, 1797) recognized that breathing pure O_2 might cause lung damage. This recognition exerted a damping influence on the therapeutic use of O_2 which, since Priestley's announcement of its possible salubrious action, had been carried to extremes not only by charlatans but also by physicians of better repute.

The first flush of enthusiasm for O_2 therapy had about died down by the end of the first decade of the 19th century, but there was a distinct resurgence some forty years later, so that shortly after the middle of the 19th century, O_2 therapy—or its handmaiden, compressed air therapy—had been reported as successful, sometimes fantastically so, in the treatment of practically every one of the maladies to which human flesh had fallen heir. This revival of O_2 therapy was particularly evident in England (Birch, 1859); and in France, Demarquay (1866) expressed astonishment that in spite of its beneficial effects described by Beddoes (1797) and others, O_2 "should have been abandoned as a curative means" and treated as a dangerous gas because of its activity in chemical combustion.

The value of O_2 as a means of combating hypo-oxemia was early recognized and its use in the treatment of pneumonia advocated (Beddoes, 1797; Golden 1866; Brunton and Prickett, 1892; Brunton, 1912; Hill, 1912 and others). Cabell, (1874) described several cases in which the administration of pure O_2 had been a life-saving measure and recommended its use even though he stated: "In general the use of the gas is held to be contra-indicated in the presence of acute inflammation." He agreed with Smith (1870b) who maintained that "When respiration is seriously interfered with, the danger from this source outweighs all risk from any possible increase of the inflammation which the use of oxygen may occasion." The method of O_2 administration at that time however was not one of continuous exposure for prolonged periods so that chances of injury from O_2 were very remote as were also, in many cases, possibility of benefit to be derived.

Fauntleroy (1916) reported that O_2 treatment in injuries from chlorine and bromine gas was distinctly beneficial. Haldane (1927) recommending O_2 for the relief of anoxemia arising from gas poisoning in World War I, cautioned that in some cases it might cause further damage in a lung already inflamed.

Stadie (1919, 1922) emphasized the relationship between the degree of hypoxemia and the mortality in pneumonia. His construction of an O_2 chamber for the treatment of this condition by O_2 in concentrations up to 65 per cent at atmospheric pressure represents one of the more careful and consistent studies made in this country on the application of O_2 in therapy. The consensus of opinion then and in the years following was that continuous exposure of an individual to O_2 in concentrations much above 60 per cent at atmospheric pressure may lead to adverse and deleterious effects on the lungs.

In support of that opinion there has since accumulated the considerable volume of evidence from animal experimentation mentioned above. Barach (1926, 1934) from his own experimental animal studies and from practical clinical experience has maintained over a period of years that "Very rich oxygen mixtures, such as those between 80 and 100 per cent, have repeatedly been shown to produce irritant inflammatory lesions in the lungs when used continuously for two or three days or more, but concentrations under 70 per cent have no such influence. Furthermore, there is no demonstrable *tendency* to produce edematous changes in the lungs when atmospheres containing less than 70 per cent oxygen are employed. The use of oxygen concentrations between 90 and 100 per cent in human beings for long continuous periods is entirely unwarranted by the present experimental data." DuBois (1929) maintained the optimum effect for O_2 administration is 40 per cent. Richards and Barach (1934) found that living for one week in an atmosphere containing 45 per cent O_2 caused no indication of irritative action on the lungs of two normal young men.

Boothby (1932) likewise has long cautioned against the use of O_2 in the higher concentrations and states that O_2 "in excess of 450 mm. corresponding to 60 per cent at sea level should be rigorously avoided."

The fact that some patients who have died of pneumonia in spite of O_2 administration have shown more extensive lung damage than those dying without O_2 treatment, might seem to indicate that such treatment was the cause of the extension, but Boothby (1932) accepts Robertson's (1932) suggestion that such results may also mean that the O_2 treatment prolonged the life of the patient so that the pneumonia was able to progress to more advanced stages. Moersch (1937) recommends the use of O_2 in concentrations of from 30 to 60 per cent and maintains that concentrations above this offer no additional value and actually may be harmful if used for any length of time, due to the irritative action on the lungs.

Evans (1927) argued that there was no proof that a normal individual is harmed by breathing O_2 in concentrations as high as 80 to 100 per cent for one or several days. He also maintained that the data from research done on normal animals are not applicable to animals or men suffering from diseased conditions of the lungs. The work of Karsner (1916) however emphasized the fact that a large percentage of so-called "normal" experimental animals are actually suffering from

sub-symptomatic lung pathology; this would certainly indicate that the adverse effects of O_2 are by no means limited to normal lungs and that animals with pulmonary lesions, as well as normal animals are adversely affected by, and may die as a result of, O_2 exposure.

It was further reported (Evans and Durshordwe, 1935) that O_2 in concentrations of from 70 to 100 per cent had nothing but beneficial effects on the lungs of pneumonia patients and that O_2 at 100 per cent administered for from one to four hours daily not only was without harmful effects but that it induced excellent therapeutic results. Considering the numerous investigations which had previously demonstrated the relief of hypo-oxemia and the beneficial effects in pneumonia induced by O_2 administration, such results were only as might be expected.

In view of the reasonableness of the use of O_2 at high concentrations in many emergencies it is perhaps unfortunate that, to support his belief in the therapeutic use of 100 per cent O_2, Evans (1939) has maintained that those opposed to an indiscriminate use of 100 per cent O_2 do so on the basis of what he calls the "healthy animal theory." Perhaps the seemingly misleading implications of Evans' argument may be sufficient excuse for its presentation here. "The healthy animal theory," says Evans, "assumes that facts concerning human beings and the lower animals are interchangeable and that data obtained by experimentation upon animals would, therefore, apply to humans. This assumption is contrary to the facts, as there has never been any uniformity in the reaction of humans and the lower animals to drugs or other therapeutic agents. . . . The second part of the theory assumes that if a given dosage of oxygen is harmful to an healthy animal, it would also be harmful to an anoxemic patient. . . . Take, for example, the dosage of insulin required for the successful treatment of diabetic coma. The dosage in these cases far exceeds the safe dosage for normal individuals. . . . The third part of the theory assumes that the tolerance of healthy animals to oxygen represents dosage for the treatment of anoxemia." The argument is obviously spurious and the analogy of insulin dosage ill-chosen.

The oxygen demands of an individual can be estimated with fair accuracy, and the O_2 needed to relieve a given O_2 unsaturation in pneumonia and similar hypoxemic conditions may be readily determined. The dilemma in the O_2 therapy of such cases, then, is not the difficulty of determining the "dosage" of O_2 needed but rather, how can the "dosage" be gotten across grossly defective pulmonary membranes and this without at the same time inducing injury.

A significant point which Evans seems to have overlooked in his insulin analogy is that insulin—fortunately enough—is not given by pouring it into the lungs; if it were, the problem of insulin administration would be similar to that in O_2 administration and the question would be—How can the desired amount of insulin be gotten to the tissues without injuring the pulmonary tissue or drowning the patient? The voluminous literature on O_2 therapy contains many reports of attempts to administer O_2 by various routes: O_2 baths; colonic, vaginal, subcutaneous, intramuscular, intravascular and intra-abdominal injections; the imbibition and enemata of highly oxygenated solutions, have all been tried—most of them more than a century ago—with the idea of by-passing the respiratory epithelium. As yet none of these attempts has been eminently successful.

Evans (1939) reported that in 1925 he had inhaled pure O_2 for four hours a day for several days without any apparent harmful effects. "This was done," he says, "in order to find a safe dosage for the treatment of disease not complicated by anoxemia." He has thereby demonstrated, notwithstanding his argument to the contrary, that he not only subscribes to, but has made practical use of, the "healthy animal theory." His claims, however, that the pneumonic lung has a higher tolerance for O_2 than a normal lung because of the fever temperature and the attendant increase in metabolism, is contrary to the observation of Faulkner and Binger (1927) and of Campbell (1937a,b) that increase in temperature increases susceptibility to O_2 poisoning.

The relative harmlessness of breathing O_2 in high concentrations for short periods would seem to be adequately demonstrated by the work of Benedict and Higgins (1911) and by the almost universal employment of pure O_2 in routine basal metabolism measurements. Hill and Macleod (1912) and Adams (1912) reported that men suffer no ill effects of breathing O_2 in concentrations of 80 to 90 per cent for periods as long as two hours. Fine, Hermanson and Frehling (1938), applying Bert's principle of washing out the tissue nitrogen by breathing pure O_2 to the removal of air and gaseous accumulations in body cavities, found no particularly adverse effects from breathing O_2 in concentrations of 95 per cent. Similarly Schwab et al. (1936) observed no pulmonary complications in encephalographic patients who had been administered O_2 in similar concentrations for periods of 3 hours to facilitate the removal of entrapped air. Boland (1940) also reported that no pulmonary trouble was noted in interrupted administrations of pure O_2 to patients. The application of these principles to remove tissue nitrogen in attempts to prevent aeroembolism in aviation has also been widely accepted as harmless. Behnke and Willmon (1941) found no adverse symptoms in man after breathing O_2 in concentrations of 99 per cent at atmospheric pressure for 17 hours.

In recent years the urgency of the use of O_2 in altitude work has led to a reevaluation of the effects of administering O_2 in very high concentrations to man. Barach and Richards (1935), in contrast with the earlier firm conviction that the use of O_2 in concentrations above 60 per cent (Barach, 1926, 1934) was dangerous, have modified the former view somewhat and now think that the use of O_2 in 100 per cent concentrations may be safe and desirable for short periods but that "the danger of oxygen poisoning resulting in pulmonary edema, which regularly occurs in animals exposed to concentrations of oxygen over 80 per cent for two to four days, should be a sufficient warning to prohibit the employment of 100 per cent oxygen to human beings for similar periods." Barach and Eckman (1941) point out that while the literature contains frequent reference to the use of 100 per cent O_2 it is not breathed as such in actual practice because of the dilution by small amounts of CO_2, rare gases, N_2, and water vapor. They agree that O_2 in percentages of from 80 to 100 per cent may be safely administered for periods of from 16 to 24 hours, but think it wise subsequently to lower the concentration below 70 per cent.

Boothby has likewise discarded his former interpretation that the use of O_2 in concentrations above 60 per cent should be "rigorously avoided" and recently

stated (Boothby, Mayow and Lovelace, 1939) that 100 per cent O_2 administered for 48 hours causes no signs of pulmonary irritation. These authors advise its use in a great variety of clinical conditions: "traumatic shock, abdominal distention, headache following encephalography, certain types of migraine, profuse pulmonary oedema, massive collapse of the lung, pulmonary embolism, angina pectoris, and some other cardiac conditions, infections due to anaerobic organisms such as those of gas gangrene and tetanus and possibly certain infections due to partially anaerobic organisms."

Armstrong (1938), having formerly cautioned against the use of O_2 at tensions greater than 456 mm. Hg, more recently reports (Armstrong, 1939) that the danger of the use of high O_2 concentrations has been overemphasized and says, ". . . recent clinical experience indicates that the human lung is more resistant [than animal lungs] to the irritative effect of pure O_2 and in a few cases it has been administered continuously for as long as five consecutive days without any apparent harmful effect." The drying and chapping of the lips, mouth and throat with occasional irritation extending down as far as the larynx and the hoarseness which has occurred not uncommonly in those using the plain O_2 tube or the open O_2 mask have been attributed to the dryness of the gas rather than to any effect of O_2 itself (Armstrong, 1939). This explanation is reminiscent of the charge made by Brüning (1912) that the O_2 effects reported by Bornstein and Stroink (1912) were caused by the dryness of the gas rather than the O_2—a charge which Bornstein (1912) later refuted.

The present tendency to dismiss the possibility that O_2 in high concentrations exerts no significantly deleterious action on man, calls for a consideration of some of the indications that the human organism is not immune to the adverse effects of O_2 in concentrations approximating 80 or 100 per cent at atmospheric pressure. Such evidence may be found *a*, in data from experimental exposures of men to pure O_2 or to hyperoxygenated air, at atmospheric pressure; *b*, in occasional reports of peculiar responses in patients or normal individuals to the shift from an atmosphere of air or low O_2 to one of pure O_2 or hyperoxygenated air; *c*, in reports concerning the effects of increased O_2 tensions in exposures to compressed air, although, as already stated, some degree of reservation is demanded in accepting such effects as those of O_2 alone.

a. *Adverse Effects of O_2 or Hyperoxygenated Air, at Atmospheric Pressure on Man.* Conclusive evidence that men may be adversely affected by breathing O_2 in increased concentrations at atmospheric pressure is presented in the reports of Behnke, Johnson, Poppen and Motley (1935) and of Behnke (1940). These investigators found that one of ten men breathing O_2 at from 96 to 99 per cent at atmospheric pressure became fatigued and had symptoms of bronchial irritation after 4 hours exposure; in another series one subject complained of substernal pain and toxic effects at the end of 6 hours' exposure. Behnke and Willmon (1941) found that tests in which 99 per cent O_2 at atmospheric pressure was employed, frequently had to be terminated at the end of 6 hours on the subject's complaint of substernal soreness, aggravated by deep inspiration; although auscultation and x-ray examination failed to reveal any alterations. The

authors maintained that the substernal distress points to the irritant property of pure oxygen and indicates pulmonary congestion and cardiac vasomotor spasm. It was further reported by these authors that impaired neuromuscular coordination and the power of attention, or an increased effort to maintain these functions, occurred after 1 to 3 hours of exposure in 3 of 4 subjects tested; hyperpnea and symptoms of lung irritation, dry cough, substernal pain and a high leucocyte count were also observed. The authors concluded, however, that healthy men between the ages of 22 and 40 can breathe pure O_2 at one atmosphere with comparative safety for 4 hours.

Anthony (1940a) maintains that breathing O_2 causes no noticeable disturbance in healthy persons, but that careful studies show that an increase in partial pressure of O_2 above normal elicits responses in the human organism as consistently as does a decrease. Prolonged administration of O_2, especially if there is an associated increase in air pressure, may cause severe or even fatal changes.

Perhaps one of the most valuable and informative contributions concerning the effects of increased percentages of O_2 at atmospheric pressure on the normal human lung is that of Becker-Freyseng and Clamann (1939). These investigators exposed themselves to O_2 (90 per cent) at atmospheric pressure for a period of 65 hours. On the second day of exposure the pulse frequency and vital capacity which had decreased initially were distinctly increased. There was also an elevation in body temperature. Paresthesias appeared in both individuals, particularly in the finger tips, spreading from the middle finger, and on the following day involved the toes. One of the subjects (B) became ill and his vital capacity then diminished progressively; pulse rate and temperature continued to rise. Pain was felt in the knees and elbows. Dyspnea became apparent but auscultation revealed nothing abnormal. The objective and subjective effects progressively increased in both individuals. The electrocardiogram showed no abnormality. On removal from the chamber the x-ray revealed no lung changes in either subject. The blood examination showed an increased R.B.C. count but the hemoglobin content was about normal. The leucocytes had increased—particularly in subject B in whom it had risen from 6200 to 12,700. Subject C felt well but the paresthesia persisted in both men for ten days. Subject B's illness which had begun in the chamber became worse on removal; he vomited, complained of nausea and headache. The following evening he was taken to the hospital; the vomiting stopped the first night, but there was a distinct bronchitis with fever. There was fluid in the right thorax and signs of bronchopneumonia but the x-rays were still negative. Three days later the fever fell and he was discharged from the hospital on the eighth day. The vital capacity continued low until the sixth week. The paresthesia described by Becker-Freyseng and Clamann suggests that the numbness of the lips observed by Hill and Greenwood (1906) during their exposure to compressed air and described by them as a "false sense of anesthesia" may very well have been an effect of the increased O_2 tension.

The numerous reports of atelectasis among the autopsy findings of experimental animals exposed to O_2 finds a counterpart in the report of Waters (1942) that in the human lung, inactive portions more readily became atelectatic when filled

with pure O_2 than when they are filled with air. The possible occurrence of atelectasis may constitute a hazard in the therapeutic use of pure O_2 where for any reason a portion of the lung is not freely ventilated or where the O_2 may be partially or completely trapped in, and subsequently absorbed from, the alveoli of that portion (see p. 147).

b. *The Response to a Shift from Air or Low O_2, to Pure O_2 or Hyperoxygenated Air.* The literature contains several reports that the shift to hyperoxygenated air following states of hypo-oxemia or low O_2 administration has resulted in peculiar and untoward reactions which are difficult to interpret except as manifestations of an inability to adjust rapidly to the higher O_2 tensions, or to some adverse action of O_2 itself.

Barach (1941) has reported that patients who had suffered for some time from anoxemic conditions frequently showed profound mental disturbances lasting several days when subjected to O_2 in concentrations of about 50 per cent at atmospheric pressure. One such patient whose arterial O_2 saturation was only 55 per cent and to whom 50 per cent O_2 was administered reached a state of complete irrationality and delirium within one hour of the initiation of the treatment. Dill (1941) discussing these observations points out, however, that residents of high altitudes are not apparently affected adversely by their return to normal atmospheres after having been acclimatized to low O_2 atmospheres. This suggests that perhaps the rate of change in gaseous composition of the air breathed may be involved.

Schwarz and Malikiosis (1938) in altitude tolerance tests found that the sudden elevation of O_2 tension after periods of hypo-oxemia resulted in deterioration and disorders of the subjects. Moody and Howard (1942) reported that O_2 administered by tent to a 2 year old child suffering pneumonia caused convulsive attacks. The first exposure was continuous for 48 hours, at the end of which time the patient was removed to room air, then returned to the O_2 at intervals for 6 days. There was original relief from the pneumonia but in one of the exposures the patient developed severe convulsions which involved the whole body, the temperature rose to 101° F. Removal from the tent resulted in cessation of the attack but dyspnea again developed necessitating the patient's return to the tent in the afternoon; this precipitated another convulsion which stopped almost immediately on being removed from the tent. The O_2 concentration was in the neighborhood of 72 per cent.

These observations are reminiscent of those made by earlier investigators whose reports would seem to have been dismissed as fiction. Birch (1859) using O_2 therapeutically observed that occasionally strange reactions were precipitated by breathing O_2 which he thought were not explainable on a psychological basis. He describes these as "... a sense of constriction of forehead and temples; a feeling of weight over the centre of the parietal bones, and in the occiput; a rush of blood to the head, fullness, pain, or oppressive sensation in the nape of the neck and base of the brain; sudden faintness; palpitation of the heart; ... violent reflex movements in extremities affected with paralysis of voluntary motion, ... a state of unnatural excitement of the entire nervous and vascular systems, which has continued for successive days. ... The chief symptoms of a disturbing

character observed from pushing very large doses of the gas are, in thin anaemic persons, sudden or gradual disappearance of the pulse, pallor of countenance, coldness, and partial collapse; in the plethoric or sanguineous the reverse—viz., too-excited circulation; full bounding pulse; intense heat of head, face, and skin; severe, oppressive headache."

Smith (1870) likewise reported that breathing O_2 sometimes produced subjective responses such as a sensation of freedom about the chest, a feeling of warmth below the sternum, occasionally a slight degree of vertigo, a disposition to yawn constantly during inhalation and an inclination to sleep. Haldane (1917) reported that the immediate effect of suddenly administering high concentrations of O_2 to a cyanosed person was sometimes unpleasant as he had observed from experiments on himself and others. Under such conditions, he says, "The heart may become tumultuous in its action and the breathing irregular. . . ," and advised against too rapid addition of O_2 to the inspired air in cyanosed patients. DuBois (1928) remarks that the symptoms of anoxemia curiously enough "are sometimes exaggerated when the subject receives oxygen and not infrequently he acts like a drunken man."

The reports of untoward reactions to breathing O_2 after exposure to low O_2 or after a prolonged period of anoxemia in disease, recall also the experiments of Haldane and Smith (1893) in which they found that subjects after rebreathing air in a chamber for several hours to a point where the CO_2 had reached 6 or 7 per cent and the O_2 had fallen to about 13 per cent, were nauseated, vomited, and suffered headache *after* their return to room air. Somewhat comparable effects were also noted in subjects after having been exposed to a gradual depletion of O_2 where the CO_2 was kept low.

Alexander, Duff, Haldane, Ives and Renton (1939) found that return to normal air or to pure O_2 after having been exposed to high CO_2 (6 to 7 per cent) for an hour, resulted in similar disturbances. It has been suggested (Haldane, 1941) that such nausea and vomiting may have been responsible for some deaths occurring in the use of submarine escape apparatus where the subject breathing a low O_2-high CO_2 atmosphere is suddenly exposed to pure air or concentrated O_2. The vomiting, he says, can be avoided by purifying the air, or by breathing O_2 or pure air for some minutes before attempting escape; this would give time for the vomiting to occur if it is going to do so.

The fact that such disturbances occur only on the return to normal air or to increased O_2 tension must represent a failure of the organism rapidly to readjust to the higher O_2 tension. But while such reactions are precipitated by the return to the increased O_2 tension, they may perhaps be considered as the delayed effects of the CO_2 or low O_2, rather than as adverse effects of the increased O_2 tension itself. The delay in the precipitation of the disturbances until after the return to normal air may then simply indicate that as a result of the gradual accumulation of CO_2 and the depletion of O_2, medullary centers may have been depressed to a point where they become incapable of normal response; then with a rapid return to increased O_2 tension the reactivity of those centers recovers before the offending chemical state of the cells has been completely rectified.

The fatigue commonly experienced after shifting from low O_2 to a higher O_2

tension deserves special mention in this connection. The fatigue felt on the return to normal air or pure O_2 after breathing low O_2 as described by Haldane and Smith, (1893) is highly suggestive of a persistence of some functional disturbance or organic damage sustained during the low O_2 exposure, the recovery from which is slow. Dill (1938), for example, points out that some of the C.N.S. effects of low O_2 may be caused by an increased intracranial pressure arising from an altered capillary permeability which as Landis (1928) has maintained occurs in O_2 lack. It is difficult to see how complete recovery from such conditions could occur immediately on return to normal air. Dill's report emphasized the persistence of fatigue effects of low O_2, although Horvath, Dill and Corwin (1943) observed no lasting harmful effects on the C.N.S. of schizophrenic patients after their exposure to anoxia severe enough to produce brief periods of unconsciousness.

In connection with the fatigue effects of low O_2 it is of interest that Monge (1943) has emphasized again that sub-acute mountain sickness is a "fatigue disease" and that exposure to high altitudes may change the capacity of the tissues to utilize O_2. Monge et al. (1928), Edwards (1936), and Barron, Dill, Edwards and Hurtado (1937) have also suggested that in low O_2 exposures there is a failure in O_2 utilization by the tissues, particularly those of the C.N.S. and that this might be caused by a change in respiratory enzymes.

Such alterations in enzyme mechanisms, especially where they are not immediately reversible, might help to explain some of the reactions precipitated by a shift from low O_2 to the higher O_2 tensions of normal air or pure O_2, and are therefore pertinent to the consideration of those responses experienced following actual or simulated flights to high altitudes. Romano et al. (1943) found that syncopal reactions persisted for some time after an individual's return to normal atmospheric pressure following simulated flights to high altitudes (35,000 ft.) in decompression chambers. In some cases the severity of these reactions which continued for as long as 24 hours, actually increased rather than decreased when the higher O_2 tension of normal air was readministered. The question arises as to just how far these syncopal reactions and the well recognized post flight fatigue represent failure of the organism rapidly to readjust to a sudden shift to an increased O_2 tension after having been "acclimatized" to low O_2 tensions. It has been claimed that post flight fatigue is due to "silent" aeroembolism (Behnke and Willmon, 1941; Behnke, 1942) but as Carson (1941) points out such an explanation is without substantial support. Certainly the evidently complex etiology of post flight reactions (MacFarland, 1941) make it appear very unlikely that they can be attributed to any one single factor alone; the enthusiasm with which aeroembolism was first grasped as the explanation for so many of the responses to high altitude conditions has not been justified by the experimental evidence.

Low O_2 constitutes the predominant stimulator for the chemo-receptors of the carotid reflex structures (Gesell, 1940). A sudden increase in O_2 tension diminishes or even abolishes the reflex drive arising in this structure, possibly as the result of a shift toward the alkaline side induced by the release of Na from the

lactate ion; now, if at the same time the sensitivity of the central regulators, the adequate stimulus for which is predominantly CO_2 (Gesell, 1940) be depressed, for example by prolonged excess CO_2, low O_2, or anesthesia, breathing and other vital phenomena will be profoundly affected. Evidence that this is so finds support in the work of Moyer (1941) in which it was pointed out that if anesthesia be of such level as to depress or abolish the response to CO_2, the administration of increased O_2 tension induces respiratory failure, and further that whenever artificial respiration is indicated during evipal or phenobarbital anesthesia, the gas mixture should not contain O_2 in concentrations of more than 40 per cent.

c. *Evidence of Adverse Effects of Increased Tensions of O_2 from Exposures to Compressed Air at Moderate Pressures.* Lorrain Smith (1899) was of the opinion that the increased O_2 tension of compressed air might play a part in the production of caisson sickness because he found some of the pathology of O_2 poisoning present also in caisson sickness. This suggestion was dismissed by subsequent investigators who had become justly convinced that caisson sickness was caused for the most part by the release of nitrogen bubbles on decompression. The deep diving and high pressure work of late years, however, has necessitated a reconsideration of O_2 poisoning as a possible contributor to the reactions observed not only during the actual exposure to the increased air pressure, but also in the subsequent decompressions.

It has become increasingly evident that it is unsafe to assume that because an increased concentration of O_2 at atmospheric pressure frequently exerts no apparent toxic action in short exposures, there would be a similar absence of effects with the same tension of O_2 in increased air pressure, where other variables are involved. For example, there is experimental evidence that the presence of CO_2 may be an important determinant in the action of O_2. Even a relatively slight increase in the CO_2 tension, whether it be due to inadequate ventilation, an altered rate of diffusion or an upset in the CO_2 carriage by the blood (see section II below) augments the toxic action of O_2. In addition to this there is the influence of the increased concentration of nitrogen.

It is entirely unlikely that the increased O_2 tension in compressed normal air, even with the high pressures now frequently employed in deep diving, would of itself cause O_2 convulsions, provided the CO_2 were kept low and the exposure not unduly prolonged, but there is evidence that such increased tension of O_2 can induce lung damage which may be partially or completely masked by the wide margin of safety provided in normal lungs. It has long been accepted (French, 1916; Haldane and Priestley, 1935; Fraser, 1940) that broncho-pneumonia following prolonged exposure to compressed air in deep diving has been caused by the increased O_2 tension in the neighborhood of 760 mm. Hg.

But besides causing lung damage, O_2 in high concentration alters the fundamental oxidative mechanisms in the tissues and this, as is also true of the lung changes, is not always rapidly reversible. These possible O_2 effects induced by compressed air, even though they be sub-symptomatic during the exposure, are worthy of consideration in relation to the problem of decompression, particularly since End (1938) claims, "An explanation of compressed air illness based entirely

upon theories of bubble formation is not altogether satisfactory," and an analysis of some of the experimental data presented by Behnke and Shaw (1937) concerning the use of O_2 in the prevention of caisson sickness strongly suggests that the problem of decompression is not always simply one of eliminating the formation of nitrogen bubbles.

The report of French (1916) illustrates the well known difficulty sometimes encountered in the safe decompression of divers but it too suggests that part of that difficulty may be attributed to incompletely or slowly reversible changes induced by prolonged exposure to increased O_2 tension. Thus the conditions would approximate those obtaining in animals which, after adaptation or "acclimatization" to pure O_2 at atmospheric pressure, show distressing symptoms when returned to normal air—symptoms which can be largely relieved by the animal's return to the O_2 atmosphere. The almost immediate improvement which commonly results from recompression treatment in many cases of compressed air illness may be due, then, not simply to the dissolution of nitrogen bubbles, but also to the re-establishment of the abnormal environment which the "acclimatization" changes in the lung or in cellular oxidative processes require for tissue function. The inclusion of this possibility as a part of the explanation of decompression difficulties does not, of course, detract from the importance of the usually accepted interpretation, viz., that of nitrogen bubble formation.

The recompression chamber has become an indispensable adjunct to all deep diving operations and occasionally prolonged recompression treatments have been employed. Haldane and Priestley (1935) remarking on the difficulty on safe decompression from compressed air, say it may sometimes be necessary to keep the patient in the recompression chamber for 24 hours or more. These long recompression treatments offer further suggestive evidence of adverse effects of O_2 on man especially since "acclimatization" to the increased O_2 tension, unlike the disappearance of the nitrogen bubbles, will progress indefinitely so long as the high O_2 tension is maintained. While recognizing the advantages of recompression treatment in compressed air illness, it would seem wise to keep in mind the possibility that prolonged exposure to the increased O_2 tension in the recompression chamber may also involve the disadvantages of augmenting the O_2 "acclimatization." This consideration is particularly apropos the use of pure O_2 at increased pressure to facilitate the washing out of nitrogen from the body.

Some of the cases of Shilling, Hawkins, Polak and Hansen (1935) in which compressed air illness was treated by recompression, are highly suggestive that pathology was induced by the increased O_2 concentration; for example, a diver suffering from compressed air illness was completely relieved by recompression to an air pressure of 75 pounds, but during the 294 minutes of the subsequent decompression he had a definite chill and began a dry unproductive cough which persisted after his removal from the chamber; his temperature was 102.4°F., pulse 108 and respiration rate 56 per minute. The x-ray examination showed irregular congestion in both lungs. The authors concluded: "These findings are not typical of pneumonic consolidation but resemble more that of an irritation. . . . Diagnosis of 'bronchitis, acute, condition considered to have been an irrita-

tive bronchitis' was made, and after nine days in the hospital condition had cleared sufficiently for discharge." Several factors may have been involved in the production of the pulmonary condition described, but the relatively prolonged exposure to an air pressure of 75 pounds which would be equivalent to 1.2 atmospheres of pure O_2 together with the nature and time of the onset of the pulmonary symptoms make it more than probable that the increased O_2 tension was an important contributor to, if not the underlying cause of, the "irritative bronchitis."

On the whole the evidence concerning the injurious effect of exposure of man to O_2 in high concentration at atmospheric pressure is at present not very voluminous but there is sufficient to indicate that O_2 does cause pulmonary damage, although there is a wide individual variation in susceptibility. Apparently no human lungs have as yet come to autopsy as a result of prolonged exposure to O_2 at atmospheric pressure so that no fair comparison can be made of the pathology induced in man with that so well demonstrated in the lungs of experimental animals.

Those who have argued the innocuousness of breathing O_2 in high concentrations have done so very largely because of their failure to observe any very pronounced symptoms of damage. It may be well, however, to emphasize the recognized fact that in most diseased conditions the initial pathology is subsymptomatic and that not infrequently the pathology must extend beyond a wide margin of safety before symptoms are grossly manifest; certainly in the oxygen poisoning in experimental animals, lung pathology precedes, rather than follows, the occurrence of overt symptoms. This, as Paine et al. (1941) suggest, may be one reason why O_2 poisoning has not been observed more frequently in the therapeutic use of high O_2 concentrations on man.

There would seem to be no question but that continuous breathing of pure O_2 at atmospheric pressure for periods exceeding 20 hours is damaging to the human lung and that even for periods as short as 4 hours some individuals of greater susceptibility may show symptomatology of lung involvement. The danger of administering pure O_2 in therapy may, however, be very largely mitigated by occasional interruption of the exposure as indicated from the animal experiments of Soulie (1939) and Paine et al. (1941). Obviously the use of pure O_2 in higher altitudes is attended with much less likelihood of danger because of the lower barometric pressure.

In summary it may be said that notwithstanding the present exigencies and the implication in some reports that continuous breathing of pure O_2 is innocuous, the accumulated evidence from animal experiments (including those on man) indicate that continuous administration of pure O_2 at atmospheric pressure, even for periods of a few hours' is attended with danger of pulmonary damage in some individuals and therefore demands the exercise of caution.

In addition to possible pulmonary injury, the administration of increased tensions of O_2, particularly in shifts from environments of low O_2, high CO_2, or both, is not infrequently attended by adverse reactions which are not readily attributable to any lung injury or irritation induced by O_2. These reactions may be

variously interpreted: (1) to an inadequacy in rapid adaptation to increased O_2 tensions, possibly reflecting in final analysis a lag in the readjustment of enzyme mechanisms; (2) the persistence of physico-chemical states in the C.N.S. which, built up gradually without gross manifestation during the exposure to low O_2 or high CO_2, give rise to overt reactions on sudden shift to O_2; (3) the continuation of reactions induced by the low O_2, after the administration of increased O_2 tension; (4) the action of increased O_2 tension on specific regulatory mechanisms such as carotid reflex structures.

The literature offers no justification for discarding the generalization that for continuous administration, the concentration of O_2 should not be much, if any, above 60 per cent. Yet in some conditions 60 per cent may be too high even for short exposures, in others 100 per cent may be too low for the end desired. It would appear that each case might best be considered individually. Where the administration of high concentrations of O_2 does seem desirable the administrator still must weigh the possible benefit to be derived, against the possible dangers to be incurred. Argument derived largely from observations on individuals possessed of wide margins of safety may be misleading but they cannot reverse the well-established sign posts which unquestionably point to the deleterious effects of the continuous administration of O_2 in high concentrations.

II. Possible complicating variables introduced by compressed air or artificial gas mixtures. The evidence presented above leaves no doubt that the increased O_2 tension of moderately compressed air exerts adverse effects on living organisms which in large part are essentially similar to those induced by equal O_2 tensions in hyperoxygenated air at atmospheric pressure but the assumption that the only action of compressed air is that of its contained O_2, demands further consideration. This demand becomes particularly insistent not only in view of the fact that very highly compressed air has been used as a means of studying the effects of O_2 at pressures above one atmosphere, but also because of the practical application of highly compressed air or artificial media in submarine and deep diving operations. An examination of the available data reveals that in some circumstances the effects of the increased O_2 tension obtaining under increased pressures are inextricably interwoven with those of other factors.

Effects of Increased Pressure Per Se. The argument, so commonly advanced in many of the early reports, that pressure *per se* exerted physiological effects, were, for the most part, concerned with the vascular system. That viewpoint was expressed by Moxon (1881) who stated: "There is one power by which blood can be sent into the vessels of the brain with certainty, and with any degree of force that may be desired, and that power is atmospheric pressure. It needs no experiment to show that great increase in atmospheric pressure must drive the blood away from the surface of the body and into any parts that are not accessible to air, such parts are the interior of the cranium and spinal cord." Essentially similar beliefs were expressed by numerous earlier authors (Babington and Cuthbert, 1863; Vivenot, 1865, 1868, and others).

This idea of the mechanical effects of pressure was also held by Smith (1886) who maintained that the beneficial effects to be derived from recompression

treatment in compressed air illness, was a more gradual release of the blood from the deeper tissues into which it had been shifted during the exposure to the compressed air in accordance with certain "laws," the first of which was, that "under high atmospheric pressure the centres will be congested at the expense of the periphery"; a "second law" stated that "firm and compact structures will be congested at the expense of those more compressible"; and a "third law" held that "structures within bony cavities are congested at the expense of all others." The blood, according to Smith, was "distributed not in accordance with physiological demands . . . but in obedience to overpowering physical force." It was suggested that a similar congestion within bony cavities occurs during the barometric pressure alterations accompanying weather changes and Smith proposed that those persons who regard themselves as "walking hygrometers" and are accustomed to say they feel the dampness in their bones, are really "barometers perhaps quite as sensitive as the instrument of Toricelli." The experiments of Poiseuille (1835), of Loewy (1895) and Hill and Macleod (1902) and the observations of Bert (1878), and Hunter (1887), however, amply demonstrate the fallacy of the claims that in compressed air the blood is mechanically squeezed from the peripheral vessels by the direct mechanical effects of the increased air pressure.

Bert concluded that the blood pressure and the increased pulmonary capacity changes, induced by exposure of animals to moderately increased air pressure were entirely due to the mechanical effects of the increased air pressure acting on the diaphragm and abdomen. This conclusion is of especial interest since in another connection Bert insisted that the only effect of increased air pressure is that caused by the increased tension of the contained oxygen. DuBois-Reymond (1899) reported that exposure to compressed air tended to lower the diaphragm but Heller, Mager and von Schrotter found no evidence that the diaphragm was lowered or that the vital capacity was increased in compressed air. More recent investigations (Hill, 1912; Shilling, Hansen and Hawkins, 1935) indicate that the vital capacity of divers is increased in compressed air.

The report of Case and Haldane (1941b) indicates that articular surfaces and synovial fluid may be physically affected by increased air pressure. "At high pressures loud cracking noises, audible to others, were frequently produced when J.B.S.H. moved his shoulder joints. Clearly the pressure between the articular surface is increased tenfold, and the effect of irregularities must be enhanced. No pain was associated with these sounds." However, because of equal distribution of pressure throughout fluids it is a bit difficult to see just how bearing pressure between the articular surfaces could be increased to this degree; the explanation offered for the audible sounds would appear to necessitate the assumption of a compressional alteration in the volume of synovial fluid, or of gas which may have accumulated in the joint capsule during previous exposures to, and decompression from, high pressures. In any case if exposure to compressed air does increase the bearing pressure on the articular surfaces it is an exceedingly important mechanical effect of pressure.

Armstrong (1938) has maintained that because of the gases dissolved, a volume of water will be "considerably" increased by a decrease in atmospheric pressure

and that since fats dissolve five times as much nitrogen as water their volume snould be even more profoundly altered by pressure changes. If, as is claimed, these volume changes are physiologically significant under reduced pressure, they might, conceivably, be significant also under increased pressures.

Ebbecke (1914) reported that increased hydrostatic pressure may of itself act as a stimulating factor in some conditions but that tissue can withstand pressures of 100 atmospheres without injury. Edwards and Cattell (1928) found alterations in the contractions of cardiac muscle when exposed to increased hydrostatic pressure and believed that the stimulating effect of pressures between 45 and 80 atmospheres is related to fundamental changes in the physical system of the tissue.

Further evidence that high pressure causes alterations in living cells is found in the work of Brown (1934). Ebbecke (1935a, 1936) regarded the paralysis caused by high pressure as a mechano-narcosis and thought it was in some respects comparable to electro-narcosis. Increased thigmotaxis and geotaxis and a tendency to rolling movements were induced in paramecium. In other work (Ebbecke and Shaefer, 1935) the action potentials of muscle and nerve were found to be altered, the excitability of nerve was increased and rhythmic responses were elicited by a single stimulus applied under the high pressure. Grundfest (1936) also reported alterations in the reaction of nerve fibre and Brown (1936) described changes in the isometric twitch under high hydrostatic pressure. Marsland and Brown (1936) and Brown and Marsland (1936) and Marsland (1939) report effects of hydrostatic pressure on ameboid movement.

Deuticke and Ebbecke (1937) discussed the chemical and physico-chemical alterations occurring in tissue exposed to high pressure. Ebbecke (1938) found that exposure to increased pressure caused frog erythrocytes to change from plate to sphere form and although the volume was unaltered thereby, there were accompanying intracellular changes.

Cattell (1936) in review of the subject of biological effects of high pressures has pointed out that it is well-nigh impossible correctly to evaluate the effects of pressure *per se* on living organisms by the use of compressible gas media because of the concomitant alteration in gaseous tension. This complicating factor may be largely, if not entirely, obviated by the use of hydraulic media and the results of experiments using hydrostatic pressure indicate that the responses of tissue may be altered by very high pressures. Fontaine (1929a,b) in experiments involving pressures ranging from about 25 to 150 kgm. per sq. cm., found that the metabolism of fish (as determined by O_2 consumption) was augmented by pressures up to about 100–125 kgm. per sq. cm.; at higher pressures it was diminished. Because this pressure range is not so very far from those encountered in deep diving it would appear unwise to hold categorically that in deep diving the high pressure *per se* exerts no effects whatsoever on physiological processes. On the whole, however, the evidence derived from hydrostatic pressure experiments indicates that those pressures which man has thus far encountered in diving operations do not demonstrably affect vital processes of the tissues themselves.

Increased pressure appreciably alters viscosity of gases and their diffusion, and

on the basis of these physical changes Thompson (1889) offered explanations for some of the effects he observed in animals exposed to compressed air; Hill and Macleod (1903) likewise pointed to these physical changes as possible contributing factors. One interesting manifestation of the effect of the increased density of the compressed air is the observation reported by Triger (1841) that air pressures of about 3 atmospheres caused an inability to whistle and imparted to the voice a peculiar nasal quality; pain in the ears relieved by swallowing was also noted. Similar observations have been noted commonly since that time (Bucquoy, 1861; Pol and Watelle, 1854; Foley, 1863; Hill and Macleod, 1903; Hill and Greenwood, 1906; Case and Haldane, 1941b). Smith (1886) in contrast to Triger (1841) reported that the sensitivity of hearing was diminished in compressed air and attributed this to the damping effect of the increased density on the functional vibration in the auditory apparatus. Interestingly enough Foley (1863) observed that his watch consistently lost time when in compressed air of a caisson, and this he interpreted as a result of the increased resistance offered by the compressed air to the swing of the balance wheel.

The report of Case and Haldane (1941b) presents evidence of the importance of the increased density of highly compressed air in respiration. At ten atmospheres the work of breathing, they say, is more than ten times greater than at normal pressure and with some types of canisters this increased resistance to breathing in compressed air was found to be "unbearable." Because of this, together with the coughing (attributed to caustic dust stirred up from the respirators by the increased turbulence in compressed air) and the lack of self control induced by the increased pressure, subjects removed their respirators when they should not have done so. The authors recommended that because of these factors all respiratory apparatus intended for use at high pressures should be tested under service conditions rather than at normal atmospheric pressure. This recommendation emphasizes the danger of assuming that the significance of a given mechanical or chemical factor in the functioning of respiratory apparatus is constant at both high and normal pressure; it would appear to be equally if not more dangerous to make similar assumptions concerning the physiological respiratory apparatus within the mammalian organism. Further mention of the physical factors of viscosity and diffusion is made below in connection with the effects of nitrogen.

The mechanical effects of increased pressure are obviously of importance where there is an absence of the normal patency of orifices leading to air pockets within the body. Smith (1886) reported that pain and other subjective responses arose from the frontal and maxillary sinuses during exposure to increased pressure because of temporary or partial blockage of the normal passages. Lack of adequate pressure equalization within such pockets may then elicit responses involving not only autonomic mechanisms but also the organism as a whole. Moreover, because the degree of patency may vary under different conditions, the magnitude of the response arising from this source is not uniformly predictable. In normal individuals trained to equalize the middle ear pressure Case and Haldane (1941) found that rapid compression, e.g., from one to seven atmospheres in 90 seconds

may be accomplished without any after effects or discomfort. This rate of pressure increase, about one-half an atmosphere in 7.5 seconds, it was pointed out, corresponds to a vertical dive in air at a rate of about 1600 miles per hour.

These same authors (Case and Haldane, 1941) did observe, however, that both pulse rate and systolic blood pressure rose in some instances and fell in others during rapid compression in air, but these changes did not appear to be related to the peculiar subjective sensations experienced on exposure to the high pressures. Carlson, Ivy, Krasno and Andrews (1942) found no significant changes in blood pressure, respiration or heart rate of dogs as a result of subjecting them to very rapid air pressure changes such as encountered by aviation personnel. Shilling and Willgrube (1937) state, "It is well known that if pressure is applied too quickly the diver becomes dizzy and often so dazed as to require several minutes to orient himself." The rapidity of onset of this effect suggested to them that some mechanical compression factor might possibly be responsible for this subjective effect.

The question of the significance of intestinal gas pockets does not assume the importance to the diver that it does to the high altitude flyer yet in some cases where considerable gas is present at atmospheric pressure, rapid compressional reduction of intestinal gas volume may affect the organism although perhaps not adversely. Snell (1896) remarked that workmen are in the habit of tightening their belts after entering the compressed air in caissons and he interpreted this as a response occasioned by the decreased volume of intestinal gas caused by the increased pressure. Incidentally, the increased volume of intestinal gas which occurs on decompression from compressed air seems to have attracted little attention although it would appear to be worthy of consideration as a possible contributor to decompressional effects.

The problem of pressure equalization in air pockets may, under some circumstances, also involve the lungs directly. Some indication of this is found in the report of Case and Haldane (1941b). One of their subjects suffered a pneumothorax as a result of three exposures to compressed air at 8.6 atmospheres. The x-ray examination, in addition to showing pneumothorax on the left side, revealed what appeared to be "emphysematous bullae at the extreme right apex." There was no evidence of tuberculosis. The thoroscopy 23 days after the last experiment showed the left lung was almost entirely collapsed. After a slow recovery there were two relapses in eight months. Although the subject was an athlete the pneumothorax was thought to have been due to the presence of congenitally weak areas in the lungs. The immediate cause of the rupture was not determined but several possible explanations were offered, viz., (a) "The lung was was over-distended while inflating the Eustachian tubes during compression; (b) The subject held his breath during a decompression, and the expansion of the air brought about the rupture"; (c) improper manipulation of valves of rebreathing apparatus, causing a sudden increase in gas pressure in the lung; (d) "A bulla with poor communication with the bronchi existed and filled up with air at high pressure. During decompression the air could not escape into the bronchi, and burst out into the pleura."

The experiments of Polak and Adams (1932) and of Adams and Polak (1933) would seem to leave little doubt but that fatalities which occurred in the use of the submarine escape apparatus in relatively shallow water (about 15 ft.) were the result of lung injury caused by the undue pulmonary distention while holding the breath during the ascent. In the light of these experimental findings, the most likely of the explanations offered by Case and Haldane for their pneumothorax mentioned above are (b) and (d). The probability of distending the lung during compression would appear to be much less than during decompression when the breath is held, unless of course some bronchi and bronchioles leading into air containing alveoli were plugged so that equalization of the alveolar pressure could be attained only by excessive stretch or rupture of adjacent alveoli in free communication with the trachea. If it be admitted that distention of the lungs, either in whole or in part, may occur on compression, one must then recognize the possibility that influences other than that of pulmonary rupture may arise from the lungs distended to points short of rupture, and that such influences may very well contribute to the responses which occur on exposure to compressed air.

This is especially pertinent to those subjective and neuro-muscular reactions which appear immediately or within a very few minutes after compression. An unequalized increase in intrapulmonary pressure may not only profoundly affect breathing but as the experiments of Luckhardt and Johnson (1928) showed, it may also affect the heart, reflexly, and by direct central asphyxia, and it may abolish the knee jerk and render the animal unconscious and anesthetized in 12 seconds.

It has also been found that increased intrapulmonic pressure alters the response of striated muscle to electrical stimulation of its motor nerve, although it has no evident effect on contraction elicited by direct stimulation of the muscle (Bean, 1942); from this it would appear that increased intrapulmonary pressure and lung distention influence the mobilization of the contractile response through some action on the neuromyal junction. Such reactions arising from pulmonary distention are more than of passing interest in connection with the submarine escape fatalities referred to above, for with the lung distention which is said to have occurred under those conditions, the resulting circulatory, cortical and neuromuscular reactions may have rendered the subjects unconscious or completely incapable of voluntarily controlling their breathing and muscular activity even in the first few seconds of the ascent to the surface.

Walsh (1941) in observations on a patient in whom there remained extensive defect in the skull following recovery from a right temporal craniotomy, found that exposure to decreased pressure (barometric pressure 247 mm Hg. and pure O_2 as the respiratory gas) caused an elevation of the scalp 1 cm. above its pre-exposure level and that return to atmospheric pressure caused a return to its original position. Exposure to increased pressure, on the other hand caused a reversible depression to 1 cm. below the level of the skull. These results were interpreted as indicating that these pressure changes had induced an alteration in the volume of cranial contents because of the pressure effects of air contained

in the cerebrospinal fluid in the ventricles, or because of changes in the amount of blood in the cerebral vessels or to an alteration in the amount of free cerebrospinal fluid within the cranium. The author states that if the cranium had been intact the intraspinal pressure, according to the experiments of Boothby and Walsh (1941) "would have increased 3 cm. in a manometer arm attached to a lumbar puncture needle."

Subjective and Neuromuscular Reactions to Compressed Air. Many of the older reports concerning the effects of compressed air emphasize the peculiar subjective effects such as sensory disturbances, feelings of intoxication and invigoration (Demarquay, 1866). Triger (1841) describes subjective changes experienced in compressed air in caisson work. Foley (1863) maintained there was considerable individual variation in the effects of compressed air on caisson workers; in some subjects the senses of taste, smell and touch were lost or dulled, and there occurred subjective states of indecision and stupefaction, feelings of intoxication, cardiac changes, tremors and motor disturbances, and in a few there was "complete demoralization."

An early description of the subjective changes experienced by divers is that given by Green (1861). The feeling of sleepiness which he noticed especially in his deeper dives (about 163 ft.) was regarded by him as particularly important for "with that symptom the diver knows he must instantly be drawn up"; peculiar visual and gustatory sensations were also noted. His report provides evidence of a certain prevalence of belief that a diver's judgment was impaired during his exposure to compressed air during a dive; from a sunken steamer he says he "sent large sums of money which *strange* to record, invariably proved me less than when under water. I called the attention of the company to this discrepancy but was politely informed that it was 'very deceiving down there you know.' "

The report of a caisson worker (Hill and Macleod, 1903c) serves to illustrate further these subjective changes in compressed air (37 lbs. gauge). "You felt a wee bit giddy when you went in. . . . I never felt happier than when I was in compressed air. Always happy, and on the cheery side. Why, laddie, I would get up feeling very dour and queer, and just go into the workings, and then whistle and sing all day long. Not that you could hear the whistling, at least a man with my lungs, when the pressure was over twenty-five." When candles were used for light—"You nodded, and didn't care if you went to sleep forever, though it was all very nice and dreamy. When I was alone in that 'casoon' I had to rope myself up, lest I should fall asleep and tumble to the bottom, 60 feet below. It was better under the river than in the casoons, because under the river the air could escape into the Thames. Tobacco had no sting. Even Irish roll had lost its savour. The only stuff that had any flavour was four-ale." Snell (1896) had also reported cases with somewhat similar response to compressed air.

Hill and Greenwood (1906) experienced sensory changes of an anesthetic nature when in compressed air—"This loss of the fine vibratile movements of the tongue and lips, a loss probably resulting from the damping effects of the dense air, leads to a false sense of anaesthesia in the former parts." Many of the older descriptions of the subjective effects of compressed air are difficult to evaluate,

especially since some of the less reliable may have been unduly tinged with the enthusiasm of over-zealous oxygen or compressed air therapeutists or their antagonists. But recent observations, amounting to a rediscovery of the subjective and neuromuscular reactions to compressed air, elevate many of those older claims, previously dismissed as incredible, to a position of validity little below that of the current reports.

Damant (1930) reported that some divers became abnormal mentally and suffered a loss of memory in deep dives (300 ft.). He also pointed out that experienced diving officers have long recognized that subtle changes in character and behavior sometimes occur in divers even at lower air pressures. Phillips (1931) presented more detailed information concerning these subjective and mental responses in deep diving. In going to depths of from 270 to 300 feet, divers "found that it was much more difficult to assimilate facts and exercise the quick decision essential for successful diving. It might be summed up as a slowing of cerebration." Some divers said that they had "passed out" when on the bottom and others felt as though they were "under an anaesthetic." Hill and Phillips (1932) and Thompson (1935) remark further on these subjective effects of increased pressure. Behnke et al. (1935) reported that in laboratory workers exposed in a chamber to air pressures as low as 4 atmospheres, there occurred emotional and neuromuscular disturbances which seriously interfered with accurate performance of simple routines in laboratory technique; no objective or subjective tests were carried out but it was maintained that these effects of compressed air are "immediate in their onset."

Shilling and Willgrube (1937) state that 5 atmospheres of air pressure induce a feeling which is likened to drunkenness. They are in essential agreement with Phillips (1931) and Hill and Phillips (1932) that there is manifest a dangerous overconfidence, accompanied by a dulling of mental ability, difficulty of assimilating facts and of making quick and accurate decisions. These authors (Shilling and Willgrube, 1937) present quantitative experimental data attesting to the slowed reaction time in mental and neuromuscular responses. They find also that increased experience materially lessens the subjective effects and that men with high mental ability do not fail as quickly as do those of lower intelligence.

Case and Haldane (1941b) in an interesting and informative series of experiments on themselves and other human subjects, found that air pressure at 5 atmospheres caused no noticeable subjective or objective changes and even at 7 atmospheres there was no deterioration of mental ability, arithmetic problems actually being performed more rapidly and with fewer mistakes. But at 8.6 atmospheres a variety of subjective reactions were observed, e.g., two individuals were slightly confused, two others were distressed and felt as if they were going to faint, one was euphoric and felt very confident, and another was mildly elated. Still another was unusually obstinate but showed no obvious emotional reaction. At 10 atmospheres two subjects were "somewhat euphoric on the first occasion, but later this wore off"; another "varied between depression and elation". At 10 atmospheres the changes were quite definite; many of the subjects reported they felt drunk. Strange sensations were felt on the lips "something like velvet."

The timing of tests, making notes and gas sampling were either not carried out or were performed only with great difficulty, and some observations made under these conditions were not very satisfactory. "It is quite imperative," these authors say, "that no great trust should be placed in human intelligence under these circumstances." The variety of effects described clearly indicates that there is no *one* subjective response which characterizes the intoxicating action of compressed air, but rather that the subjective reactions may vary widely in different individuals.

In contrast to statements of Behnke and Yarbrough (1938) Case and Haldane (1941b) maintain, "It is quite incorrect to say that people are stupefied at such pressures. . . . However, they are definitely less responsible than when normal." The latter authors also found that the symptoms reached a maximum within 2 minutes of compression and did not increase after 30 minutes at 10 atmospheres. It was thought there might have been a "slight degree of habituation" but this, it was admitted, might have been purely psychological. The higher intellectual functions of the brain were apparently more profoundly affected than those involving muscular skill. Decompression to 5 atmospheres almost always caused an immediate feeling of subjective improvement.

Air at 8 atmospheres was found to taste "harsh, metallic and indefinable" (Case and Haldane, 1941a), and this was thought to be the taste of the concentrated nitrogen rather than of the O_2. Green (1861) had apparently experienced a similar taste at much lower air pressure but explained it thus: "The pumps which were used for forcing air into the armor were of brass and with each movement of the pump I could plainly taste and smell the copper in the atmosphere I breathed." In view of the fact that subjective and sensory changes and impaired judgment occur at increased pressures, one may perhaps question whether these gustatory effects reported by Case and Haldane and by Green may not represent disturbances in the more central parts of the sensorium rather than true sensibility arising from receptor stimulation by the increased concentration of the compressed gas.

Proposed Explanations for the Subjective and Neuromuscular Reactions to Compressed Air. Various explanations have been offered for these subjective and neuromuscular reactions experienced in exposures to compressed air sometimes referred to as compressed air intoxication; one of the earliest of these was that the increased O_2 tension was the cause. The rediscovery and current re-emphasis of the importance of these reactions, has brought forth several newer explanations; some authors have held that they are of psychological origin and others have concluded that they are due solely to a narcotic action of nitrogen. An inspection of the data reveals that none of these is in itself an entirely satisfactory explanation of the phenomena and that additional etiological factors must be considered.

1. *Increased O_2 tension as the cause of the reactions to compressed air.* Triger (1841) pointed out that physical exertion could be carried out with less breathlessness and discomfort in compressed air than in air at ordinary pressure. Furthermore the subjective effects of compressed air such as the feeling of invigoration and well being were claimed by therapeutists to be the same as those

induced by breathing O_2 and it was therefore claimed by many (Demarquay, 1866) that the effects of compressed air were simply those of the increased O_2 tension. Birch (1859) reported that breathing O_2 at atmospheric pressure caused subjective and objective reactions in some individuals and maintained that these were not of psychological origin.

Bert (1878) provided more substantial support to the belief that the effects of compressed air were due to the increased partial pressure of O_2. He made the generalization that the effects of breathing air at 5, 10 and 15 atmospheres were the same as those induced by breathing O_2 at 1, 2 and 3 atmospheres respectively, and having convinced himself of the verity of this generalization, utilized compressed air to attain the desired high O_2 tensions in his studies on O_2 poisoning. Since Bert's time, the assumption that the responses to compressed air (barring, of course, those of decompression) are caused only by the increased O_2 tension, has been rather widely accepted (Bornstein and Stroink, 1912; Achard, Binet and LeBlanc, 1927; Binger, Faulkner and Moore, 1927; Cleveland, 1925; Smith, Heim, Thomson and Drinker, 1932).

Hill and Macleod (1903c), however, made the important observation that the effects of exposure to compressed air are not the same, but are actually more damaging than those elicited by pure O_2 or by an equal partial pressure of O_2 at atmospheric pressure. Similar findings have been reported by Orzechowski and Holste (1938). These results, contrary to the conclusion of Bert, are particularly noteworthy because they mean, of course, that the presence of nitrogen, the rare gases, or some physical or chemical feature of compressed air either enhances the deleterious effects of O_2 or contributes in an additive manner to those effects.

The rate of change in the environmental O_2 tension may have some etiological significance in the occurrence of the reactions of compressed air intoxication. Certainly if the shift from low O_2 or normal air, to high O_2 at atmospheric pressure elicits subjective and neuromuscular reactions (see preceding section), there would seem to be no good reason to exclude the possibility that somewhat similar reactions might occur as a result of a sudden shift from the low O_2 or normal air at atmospheric pressure to the high O_2 tension of highly compressed air; indeed, the work of Hill and Macleod (1903c) would justify the expectation that such reactions induced by a sudden shift to increased O_2 tension might be augmented by the association with compression.

Damant (1930) was of the opinion that the subjective changes experienced by divers at depths of 300 feet were attributable to the increased partial pressure of O_2.

2. *Psychological factors as the cause of the subjective and neuromuscular reactions.* The subjective character of the reactions to compressed air suggests the possible involvement of psychological factors in their etiology and several references do point to the probable importance of such factors. That psychological and emotional influences were operative in the experiments with air pressures of about 60 pounds carried out by Hill and Greenwood (1906) is implied by their statement of having felt a "false sense of anaesthesia" and by the written comments of one

subject that he was "very nervous all through the experiment" and that there were "feelings of nervousness at being exposed to so high a pressure (which at times was somewhat acute especially when we were not engaged in analytical work)."

Phillips (1931) studied the responses to compressed air in some detail by psychoanalytical methods. This investigation uncovered considerable evidence that the mental stability of the individual played an important part in determining his reaction to the increased air pressures met with in diving. It was found that those men who had experienced untoward reactions either in deep or shallow water were "of the suppressed types, who habitually exercise control. Shy, reticent, and self-contained, they work best by themselves and do not relish observation. They are usually of a philosophic rather than a practical disposition." Phillips maintained that the cause of the divers' failure was claustrophobia. The importance of psychological elements is further suggested by the fact that some authorities have indicated that in the selection of men for deep diving, very complete psycho-analyses should be made.

One of Phillips' subjects, in commenting on the response to compressed air in an experimental chamber and that experienced in actual diving, said, "You cannot possibly compare the two conditions; in London in the chamber it was light and there were others with me; on the bottom it is dark and lonely." This statement is particularly arresting, not only because it points to the significance of psychological factors in the reaction to compressed air, but also because it emphasizes the fact, so commonly ignored, that the physico-chemical adjustments of psychological origin obtaining in the organism, and upon which the effects of the increased gas tension are superimposed, are by no means always the same in the experimental chamber as they are under actual diving conditions.

Hill and Phillips (1932) also indicate that claustrophobia is the cause of the subjective disturbances met with in diving. End (1937) likewise points to this as a factor of some importance. Thompson (1935) accepts the view that these reactions are of psychological origin since, as the diving trials continued, the reactions were less intense. Similar observations of Shilling and Willgrube (1937) that training diminishes the intensity of the response and that men of high mentality do not fail as quickly as those of lower intelligence further suggests the involvement of psychological factors. The report of Fraser (1940) emphasizes that "a nervous disposition" or "nervous instability" disqualifies an individual for deep diving because these are "bound to crop up in prolonged work, especially in deep water." The observations of Case and Haldane (1941b) that on a first compression the change in consciousness is very striking and "alarms some people" but that "when it is taken for granted it is likely to have less effect on behaviour," and that there might have been some "slight degree of habituation" to the effects, or that such an impression of habituation may have been "purely psychological," attest again to the possible significance of psychological factors. Mosso's investigations led him to the conclusion that apprehension so affects the nervous system that it "aggravates in an unexpected way" the influence of changes in barometric pressure; the data concerning the effects of compressed air

seem to warrant the extension of that conclusion to include not only low barometric pressure, but also increased barometric pressure.

It would appear then that psychological factors cannot be completely dismissed in a consideration of the possible contributing causes to the subjective and neuromuscular disturbances experienced in exposure to highly compressed air, for psychological changes, which, in themselves may not be grossly manifest, might yet contribute indirectly to the effects of compressed air by providing a background of a peculiar milieu or physico-chemical adjustment which enhances or modifies the reaction to the more immediately responsible agents which are superimposed upon it.

3. *Nitrogen as an etiological factor.* It was inferred by Behnke, Thomson and Motley (1935) that the subjective and neuromuscular disturbances induced by exposures to compressed air were caused by nitrogen which at pressures as low as 3 atmospheres was said to act as a narcotic. The subsequent implied acceptance of this inference as fact, calls for a consideration of the experiments and argument upon which it was based.

An examination of the data presented as evidence of nitrogen narcosis reveals it to be unconvincing for a number of reasons; the first of these concerns the reaction selected as the criterion of narcosis. It was reported (Behnke, Thomson and Motley, 1935) that euphoria was experienced by a group of laboratory technicians working in compressed air at pressures of 3 atmospheres; and since no euphoria was observed in earlier experiments on subjects exposed to pure O_2 at atmospheric and higher pressures, it was inferred that the euphoria experienced in compressed air could not have been due to the increased O_2 tension and that it must therefore have been caused by the nitrogen acting as a narcotic. The report of other authors (Case and Haldane, 1941), however, clearly indicates that in the psychological response to compressed air there are wide individual variations and that while euphoria does occur, there are equally impressive states of depression. Moreover, breathing pure O_2 has been repeatedly reported, particularly in the older literature (Demarquay, 1866), to give rise to a sense of elation and euphoria. The presence of euphoria, therefore, does not appear to be a reliable differential symptom or an adequate criterion of narcosis.

In the second place, the evidence of Behnke et al. is unconvincing because the experimental subjects exposed to the increased O_2 tension and who failed to experience euphoria under those conditions, were evidently not the same as those exposed to the compressed air. In the third place, the experimental conditions were not at all comparable. The subjects exposed to increased O_2 tension wore masks or diving helmets during the several hours of each exposure, whereas those exposed to compressed air wore no mask or helmet and were free to move about while performing routine laboratory techniques in the company of their associates. It would seem that where such an intangible criterion as euphoria is concerned, all experimental conditions must be rigorously controlled before any inference can safely be drawn from the results.

A conclusion that the subjective and neuromuscular reactions to compressed air are caused by a narcotic action of nitrogen obviously demands the rigid exclusion

of other possible causes. Now in order to rule out increased O_2 tension as the possible cause of, or contributor to, the reactions in question, it has been assumed that the reactions to a given tension of O_2 in compressed air are no different from those induced by the same O_2 tension at atmospheric pressure. Such an assumption is based on the premise that an identical state of the tissues obtains under each of these two experimental conditions. But if the nitrogen in compressed air is a narcotic, how can the state of the tissues exposed to compressed air even remotely approximate that which obtains in an environment in which there is an equal O_2 tension but an absence of nitrogen? Comparable tissue states are not provided in these two situations and the possible involvement of O_2 as an etiological factor is therefore not satisfactorily ruled out. The argument of Behnke, Thomson and Motley (1935) appears then to be one in which the final inference or conclusion that nitrogen is a narcotic, disproves an essential premise of identical experimental conditions upon which that argument must be based.

The experiments of Hill and Macleod (1903c) as already mentioned, do indicate that the effects of compressed air are not simply those of the increased O_2 tension alone: Compressed air was found to be more damaging than those of an equivalent O_2 tension in the absence of compressed air, but even such difference does not justify a conclusion that the greater damage in compressed air is caused by nitrogen.

Another feature of the argument presented as supporting evidence of "nitrogen narcosis" was that the effects of compressed air, unlike those of increased O_2 pressure, were immediate in their onset and did not become progressively more severe as the exposure was continued. This does lend some substantiation to the view that the effects of compressed air are not simply those of increased O_2 tension, but like the results of Hill and Macleod (1903c) it provides no evidence that nitrogen at increased pressure is a narcotic. In fact, as Shilling and Willgrube (1937) have pointed out, the immediacy of the onset of the pressure effects and the absence of any increase in their severity as exposure is prolonged, constitute rather strong arguments against a narcotic action of nitrogen.

While the evidence up to this point fully justifies a conclusion that the reactions to compressed air are not simply those of the equivalent O_2 tension at atmospheric pressure, and that compressed air must involve some factor of physiological importance other than the increased O_2 tension, it offers no substantial support for the interpretation that the compressed air reactions in question are caused by the increased tension of nitrogen or that nitrogen at these tensions acts as a narcotic. Shilling and Willgrube (1937) pointed out that "the true cause of the slowed mental and neuromuscular activity encountered in high air pressure work has not been satisfactorily demonstrated."

The experimental work with helium, however, does provide some suggestive evidence that nitrogen contributes to the production of the subjective and neuromuscular reactions of compressed air intoxication. In 1919 it was suggested (Thomson, 1927) that helium, because of its physical properties, might be used to advantage in diving. At about the same time Cooke applied for, and was later (1923) granted a U.S. Patent for a method of using helium in pressure work (Yant, 1927). Since the experimental work of Sayers, Yant and Hildebrand (1925) and

the granting of a patent to these investigators in 1927, little or no practical application of helium in pressure work was made until after the test demonstration carried out under actual diving conditions by End (1937) and his collaborators. Its use then became more widely advocated (Behnke and Willmon, 1939, 1940; Fraser, 1940). The chief benefit claimed for the use of helium was that it permitted a very rapid decompression; although Case and Haldane (1941) not only reported that at pressures of ten atmospheres the use of helium failed to prevent bends but also pointed out that because of its solubility characteristics it is erroneous to expect that it should. "It is certain," these authors say, "that a mixture of this kind [85 per cent He and 15 per cent O_2] cannot be regarded as superior to air as a prophylactic against bends."

But in addition to the facilitation of decompression resulting from the use of helium, End (1937) reported that the subjective and neuromuscular disturbances experienced in highly compressed air were absent in those exposures in which helium was substituted for the nitrogen of the respired air. Similar observations were made by Behnke and Yarbrough (1938). These results were highly suggestive that nitrogen was somehow causally involved in the subjective effects induced by compressed air.

The experiments of Case and Haldane (1941b) using O_2-N_2 mixtures at pressures of about ten atmospheres demonstrate that the subjective effects of compressed air may occur even when the O_2 partial pressure is reduced to or even below the normal 20 per cent of one atmosphere. Convincing evidence is thus provided that an increased O_2 tension is not essential to the occurrence of the subjective disturbances experienced in compressed air. The experiments in which not only He-O_2 but also H_2-O_2 mixtures were used, indicate that the presence of nitrogen contributes directly or indirectly and in large measure, to the occurrence of those disturbances. The authors interpret their data to mean that the intoxicating influence of air at high pressures is the result of a direct effect of nitrogen on the brain itself and thereby subscribe to the "nitrogen narcosis" hypothesis. They maintain, however, that this narcotizing action of nitrogen cannot be adequately explained on the basis of its chemical properties or its lipoid solubility and suggest that intra- or extra-cellular adsorption processes may be the explanation of the direct nitrogen effects.

The experimental data at this stage conclusively show: that the subjective and neuromuscular reactions to compressed air cannot be attributed to increased O_2 alone; that these reactions may even occur in the absence of an increased O_2 tension; and that the presence of nitrogen at increased pressure contributes to the occurrence of these reactions. But the interpretation that nitrogen of itself acts as a narcotic still awaits proof; other factors which might contribute to the precipitation of the compressed air reactions have not as yet been satisfactorily ruled out. It would appear, therefore, that until further and more substantial evidence is presented which indicates otherwise, "nitrogen narcosis" would best be considered a hypothesis. On the other hand, there are now a goodly number of indicators which point to another, and perhaps more plausible, explanation for the reactions to compressed air than that of "nitrogen narcosis."

4. *Carbon dioxide as an etiological contributor.* Although Hill and Phillips

(1932), convinced of the importance of psychic factors, dismissed both O_2 and increased CO_2 as possible etiological elements in these peculiar compressed air effects, a consideration of the accumulated evidence reveals there is a very high probability that CO_2 is causally involved and to such an extent as to render resorting to the "nitrogen narcosis" hypothesis for an explanation, quite unnecessary. One of the more significant reports in this connection is that of Behnke and Willmon (1939). These authors were unable to distinguish the effects of breathing increased CO_2 by their subjects when exposed to increased air pressure, from those of "nitrogen narcosis." In fact they found that increased CO_2 simply increased the intensity of the "nitrogen narcosis," and said: "While we were aware of the symptoms of nitrogen narcosis at a depth of 240 feet, we were surprised at their intensity. For the application of pressure in a chamber equivalent to a depth of 240 feet elicits reactions of considerably lessened severity."

"Additional diving tests indicated that the difference in reactions between chamber and deep-sea diving could be attributed to the increase in carbon dioxide concentration in the diver's helmet."

"The symptoms, however, were not typical of high carbon dioxide tension in the lungs but rather of air at a depth of 300 feet or more. Increased depth of respiration, for example, did not precede loss of consciousness."

"Apparently the increase in carbon dioxide augmented the narcotic action of nitrogen."

These observations recall the great emphasis which Snell (1896) placed on the importance of the removal of CO_2 from caissons by very thorough ventilation and the advice of DuBois (1928) concerning CO_2 removal in diving operations. Davis (1935) has also stressed the dangers of even very small amounts of CO_2 under such conditions.

It is generally recognized that a large excess of carbon dioxide may diminish rather than augment breathing: An absence of an increased depth of respiration cited by Behnke and Willmon (1939), then, provides no justification for dismissing the possibility that the response in question could have been caused by the increased CO_2 especially in the presence of other variables, for it is widely agreed that the reaction to CO_2 may be modified by a variety of conditions, particularly by an increased O_2 tension (Bert, 1878; Hill and Flack, 1908; Gesell, 1923; Shaw et al., 1934; Haldane and Priestley, 1935; Case and Haldane, 1941). The observation that under some conditions increased CO_2 tension in the presence of increased O_2 tension not only fails to increase breathing but actually decreases it (Marshall and Rosenfeld, 1936; Dripps and Dumke, 1943), is of interest in this connection. It would appear, therefore, to be quite erroneous, and in some cases even dangerous, to assume that the response to a given CO_2 increase in highly compressed air should be the same as that induced by an identical CO_2 increase in air at normal pressure.

According to Haldane and Priestley (1935) excess CO_2 even at atmospheric pressure in addition to causing ataxia, stupefaction, anesthesia and loss of consciousness has a "narcotic effect" which "quiets down respiration." The narcotic and anesthetic effects of carbon dioxide were noted and remarked upon by

several earlier investigators (Ewart, 1794; Beddoes and Watt, 1796; Bert, 1878; Foy, 1889, 1892; Hill and Flack, 1908); and Simpson (1872), aware of its reputed effects, considered the use of CO_2 as a practical anesthetic. Wolff, Cobb and Fremont-Smith (1931) too, have emphasized the narcotic action of CO_2 and believe that some of the effects of administering an O_2-CO_2 mixture to psychiatric patients may be caused by such narcotic action. The reports of Gellhorn and Spiesman (1935a,b) that CO_2 causes auditory and visual disturbances also suggest that sensory changes which occur in compressed air could possibly be caused by an increased CO_2 tension.

Barcroft (1938) reported that breathing high concentrations of CO_2 at atmospheric pressure caused subjective and neuromuscular changes referable to an action on the highest part of the C.N.S., mental changes, and errors in manipulations requiring nicety of co-ordination such as the taking of gas samples. "Now the interesting point," he says, "is not that these errors occurred, though that is quite significant, but that I could have gone into a court of law and sworn that one at least of the two [samples] was correctly taken.... When I came out I was retaining my grip of things only with an effort." The similarity between these effects and those attributed to "nitrogen narcosis" appears to be more than coincidental.

Although Case and Haldane (1941b) found that the intoxicating effect of compressed air was enhanced by the addition of CO_2 and stated that the combined effects of high partial pressure of N_2 and CO_2 were much more severe than those of either alone, they had no explanation as to "why CO_2 and N_2 excess appear to co-operate...." These observations point again to the possible identity of "nitrogen narcosis" and the effects of excess CO_2. The authors noted further that when the partial pressure of CO_2 in compressed air rose above 3 per cent of an atmosphere, breathing was increased, but any subjective distress caused by breathing still higher partial pressures was much less than that at atmospheric pressure. This, the authors suggested, might have been due to the narcotic effect of nitrogen; but in view of the fact that excess CO_2 may, under some circumstances, diminish breathing and that it exerts a narcotic influence, it appears unnecessary to resort to an hypothetical "nitrogen narcosis" for an explanation.

The experiments of Case and Haldane (1941b) again illustrate the fallacy of assuming that the effects of a given tension of CO_2 in compressed air are always quantitatively and qualitatively the same as those induced at atmospheric pressure. The increased potency of CO_2 acting in compressed air was demonstrated by the finding that air at 10 atmospheres containing 0.4 per cent CO_2 (i.e., a partial pressure equivalent of 4 per cent of one atmosphere) caused marked deterioration in manual dexterity and mental confusion; in concentrations of from 6.6 to 9.7 per cent of an atmosphere, it caused a loss of consciousness in from one to five minutes. Significantly enough this loss of consciousness "in almost all cases ... took place quietly and easily," indicating again that it is erroneous to expect that excess CO_2 in compressed air should invariably cause hyperpnea. At atmospheric pressure, on the other hand, these authors found that 3 to 4 per cent CO_2 caused no deterioration in either manual or arithmetical skill and some

subjects showed no deterioration even with 6 per cent CO_2. They concluded that the CO_2 should be kept below 0.3 per cent in air at 10 atm. pressure.

Psychological effects and changes in emotional states were also experienced when breathing CO_2 while under increased air pressure and perseveration was noted in some subjects. One of the more notable psychological symptoms was that of euphoria and elation but states of depression, fear, and loss of memory were also reported. Such reactions correspond surprisingly well with the psychological effects which have been described (Behnke, Thomson and Motley, 1935) as typical of the reactions to compressed air and which have been attributed to "nitrogen narcosis."

A consideration of the evidence, then, reveals not only a high probability that CO_2 is an important contributor to, if not the chief cause of, those reactions which have been attributed to a narcotic action of nitrogen, but also, because the effects of CO_2 are so markedly enhanced by a compression of the respiratory medium, that the results of experiments with increased CO_2 tension at atmospheric pressure do not safely exclude CO_2 as an etiological factor of those reactions.

5. *Physical factors in relation to CO_2 effects.* Although Case and Haldane (1941b) observed that at increased air pressure the resistance to breathing through canisters was at times "intolerable" they concluded that the physical properties of the gases in the gas phase could not account for the subjective effects induced by compressed air. This conclusion was supported by their finding that in shifting from various He-O_2 and H_2-O_2 mixtures to air and to N_2-O_2 mixtures at the same high pressure, the onset of the subjective effects was not immediate but rather was delayed for a few minutes. The possible influence of physical factors, however, deserves a re-evaluation, not so much because of any direct physical action which the diluent gases for O_2 may have on the organism, but rather because of the influence which the physical properties of those gases may exert indirectly by their effect on CO_2 as an immediate causative agent of compressed air intoxication.

The short delay (1 to 3 min.) in the onset of the subjective response to compressed air stressed by Case and Haldane (1941b), the immediate onset emphasized by Behnke et al. (1935), and the observations of Shilling and Willgrube (1937) leave no doubt but that the subjective effects of compressed air are rapid in their onset. This rapidity of onset has been stressed as one of the characteristics of "nitrogen narcosis," yet this rapidity of onset serves as well or even better as evidence in support of the interpretation that CO_2 is the etiological agent in compressed air intoxication.

A consideration of this characteristic of the reaction reveals that the rate of compression assumes particular significance both in the rapidity of symptom onset and the severity of those symptoms, even though any possible effects of pressure *per se* on the tissues or compressional effects on gas pockets in the body be excluded. In very rapid compression the movement of the compressional air into the lung during the process of pressure equalization will completely prevent the exhalation of any alveolar air in spite of the respiratory movements—a simple experimental observation which the reviewer has made on numerous occasions.

Under such conditions the alveolar CO_2 which would normally find its way out into the alveolar ducts and terminal bronchioles, will be pushed back into the alveoli so that even the dead space may not be available for diluting the alveolar CO_2 the tension of which will thereby be increased. In the meantime the flow of CO_2 into the alveoli from the venous blood will have continued. The resultant sharp rise of alveolar CO_2 tension will have reached a maximum just at the end of the compressional period. But before that time the CO_2 tension of the tissues will have been appreciably elevated due to the damming up of the CO_2 in the lungs and this, associated with a concomitant increase of O_2 tension in the compressional air should be rapidly reflected in both subjective and objective changes in the subject. An early manifestation of symptoms is exactly what might be expected. This sequence of events provides a very feasible explanation, then, for the dizziness and other subjective reactions which as Shilling and Willgrube (1937) point out occur in divers when rapidly compressed.

The possible influence of the compressional inflow on alveolar CO_2 tension is brought out by the following simple calculation: If it be assumed that the volume of the residual and supplemental air in a man is 2500 cc. and that it contains 5.5 per cent CO_2, there will be 137.5 cc. of CO_2 left in the lungs at the end of a normal expiration. If further, the CO_2 in the expired air be taken as 4. per cent, the tidal air as 500 cc. and the respiratory rate as 18 per minute, there will be expired 360 cc. of CO_2 each minute under normal conditions at rest, and if the organism be in a steady state, 360 cc. should represent the amount of CO_2 poured into the lungs from the blood each minute. Now if compression in air (0.04 per cent CO_2) is rapidly carried out to ten atmospheres there will enter the lungs, 9×2500 cc. of air (assuming the lung volume itself is not changed) and this will add 9.0 cc. of CO_2 to that already in the lungs. If it takes 3 minutes to raise the pressure to ten atmospheres, at the end of compression, other things remaining constant, there will be a total of $137.5 + (3 \times 360) + 1226.5$ cc. of CO_2, in the alveolar air. If this air in the lung were at atmospheric pressure, the CO_2 would only be 4.9 per cent, but in terms of partial pressure at ten atmospheres in the lung it will be 372.85 mm. Hg, whereas normally it is less than 50 mm. In other words as a result of this compressional inflow the alveolar CO_2 tension will have been increased by about 700 per cent. Other things, however, are not constant; for example, as the CO_2 accumulates in the alveoli the diffusion gradient is lost so that CO_2 does not leave the blood at the rate of 360 cc. per minute and is dammed back in the tissues; but on the other hand the diver under actual diving conditions is not in a basal state so that the CO_2 production is appreciably greater than that during rest as the above calculation assumes.

There is another condition which contributes to an elevation of the alveolar CO_2 tension during rapid compression not taken into account in the above sample calculation but which assumes considerable importance. The advance of the compressional inflow air into the respiratory tree pushes the alveolar air ahead of it back into the alveoli. This would mean that if the interface between the advancing compressional inflow air and the alveolar air were well defined, the CO_2 tension of the gas in immediate contact with the alveolar wall at the end of a

compression to 10 atmospheres would be 10 times that which obtains under conditions of normal atmospheric pressure. In other words, if the alveolar CO_2 were 5.5 per cent at atmospheric pressure, the CO_2 tension of the gas in immediate contact with the alveolar wall at the end of the compression would be equivalent to that of a 55 per cent alveolar content at atmospheric pressure. It is hardly likely however that the interface between the inflow and alveolar air is discrete, but even though there be some mixing of the inflow and alveolar air during the compression such mixing cannot be immediate and the CO_2 tension in contact with the alveolar wall must be elevated appreciably by this factor for at least a short time.

In discussing compressional inflow there is in addition to the rapidity of the symptom onset, another peculiar feature of compressed air intoxication which is of interest, viz., that after having attained the early maximum (within 2 or 3 min.) the symptoms do not increase in severity as the pressure is maintained but may actually decrease in severity (Shilling and Willgrube, 1937; Case and Haldane, 1941b). This feature, as Shilling and Willgrube have pointed out, casts serious doubt on the "nitrogen narcosis" hypothesis. Yet in terms of CO_2 and the compressional inflow it finds ready explanation as follows: Once actual compression has stopped, the compressional inflow stops, the removal of alveolar CO_2 is then resumed, tissue CO_2 is consequently diminished and a subsequent decrease in severity of symptoms might then be expected.

The rapidity of compression to a given pressure determines not only the *rate* of compressional inflow and thereby the degree of blockage to the CO_2 exhaled from the alveoli, but also the *length of time* over which that blockage is operative and thereby the amount of CO_2 which will accumulate in the alveoli from the venous blood. The effects of both the compressional inflow and its cessation, therefore, should not be limited to only the very rapid compressions; even in the slower compressions they would appear to be significant.

Another characteristic of compressed air intoxication which has been accepted as a peculiarity of compressed air intoxication (Case and Haldane, 1941b) is the remarkably rapid disappearance of the symptoms on decompression. But this characteristic, too, may be explained in terms of CO_2. It is known that in the presence of increased O_2 tension even a small increase in the CO_2 tension has a much more pronounced effect than it does under normal conditions (Gesell, 1923); it follows therefore that the removal of a relatively small amount of CO_2 and the concomitant lowering of the O_2 tension which occurs on decompression should cause a sharp decline in severity of the symptoms. On decompression the alveolar CO_2 is being removed not only by the respiratory movements but also by a decompressional outflow of alveolar air; the alveolar air and its contained CO_2 is, in effect, being sucked out of the alveoli by the drop in the environmental pressure. The CO_2 diffusion gradient at the lung is thereby sharply increased and this in turn should result in a more rapid removal of CO_2 from the tissues.

The report that the response to compression in a He-O_2 mixture was less severe than that experienced in air (Case and Haldane, 1941b) might at first appear to be valid evidence against the inclusion of compressional inflow as a contributory

factor to the occurrence of compressed air intoxication. It must be recognized, however, that a fair comparison of the influence of compressional inflow of a He-O_2 mixture with that of air can be made only where the rates of compression and the O_2 supplied to the tissue are identical. Because the experiments of Case and Haldane, just cited, were carried out for other purposes, no rigid control of the identity in compressional rates was made; furthermore, the O_2 content of the He-O_2 mixture used was 15 per cent as compared with the 21 per cent of air—a difference which of itself is of considerable importance where the effects of CO_2 under increased pressure are concerned. These He-O_2 experiments therefore provide no reason to doubt the importance of the compressional inflow.

In any case it is particularly significant that the use of a He-O_2 mixture did not completely eliminate the intoxicating effects of compression as it should have done if those effects were due to "nitrogen narcosis." Moreover the effects which were experienced "passed off," as would be expected according to the CO_2 theory, with the cessation of the compressional inflow. Further reasons why these He-O_2 experiments do not provide conclusive evidence of "nitrogen narcosis" are presented below in another connection.

In addition to compressional inflow and decompressional outflow, there are other physical factors deserving of consideration as possible contributors to the occurrence of compressed air intoxication, namely, diffusion resistance, gaseous density and viscosity, all of which gas properties must influence to some degree the removal of CO_2 from the lungs.

Snell (1896) maintained that the increased density of compressed air decreases the diffusion of CO_2 and for this reason advocated particularly efficient ventilation of caissons. The relative importance of the process of diffusion in the exchange of O_2 and CO_2 between alveoli and trachea under various respiratory conditions is exceedingly difficult to evaluate accurately, especially since the degree of respiratory distention is not uniform throughout the lungs and varies with changes in the type and depth of breathing. Dean and Visscher (1941) state that "it seems unlikely that diffusion is directly involved in actual mass movement of air in the lung" but this interpretation of "mass movement" of air does not rule out the probability of CO_2 and O_2 exchange by diffusion processes in the alveoli and terminal parts of the lungs. Draper and Whitehead (1944) reported, however, that in respiratory arrest induced by pentothal sodium, the diffusion alone, was sufficient to supply the O_2 needs if the environment were largely that of O_2 and that the presence of N_2 either in the respiratory tract or in the environment impeded this diffusion. The outward diffusion of CO_2 was found to be slower than that of O_2.

If it be granted that the interface between the inspired air and that in the alveoli is of spike shape (Henderson et al., 1915) the gaseous exchange between the axial flow and that in immediate contact with the respiratory epithelium of the terminal bronchioles, alveolar ducts and alveoli, must be accomplished to a large extent by the relatively slow process of diffusion. DuBois (1928) accepts the view that the gaseous exchange between alveoli and bronchioles is one of diffusion. But even though one be unwilling to agree with this view without considerable reservation, there can be little doubt but that any diffusion which does

occur within the lungs will be affected when the pulmonary gas is highly compressed.

The experiments of Haldane, Kellas and Kennaway (1919) show that changes in total pressure do influence diffusion resistance and gaseous exchange at the lungs; these authors found that the effectiveness of a given alveolar O_2 tension was enhanced by a reduction in the total pressure. It is therefore not entirely correct to assume that a 2 per cent O_2 mixture at atmospheric pressure will, when compressed to ten atmospheres, supply the tissues with the same amount of O_2 as that provided by a 20 per cent O_2 mixture used at atmospheric pressure; this is a point of some pertinence to the making of respiratory gas mixtures for use at high pressures.

If an alteration in diffusion resistance affects the O_2 supply it must also affect the removal of CO_2, and any interference with CO_2 removal will contribute to the induction of compressed air intoxication. Since very small amounts of CO_2 acquire a peculiarly high potency in compressed air or increased O_2 tensions, even those changes in diffusion resistance which under ordinary conditions would be inconsequential, cannot be dismissed as insignificant in compressed air. Although argon is an inert gas and has been considered insignificant biologically, at least when present in such minute quantities as found in normal air, its physical properties (an atomic weight almost three times that of nitrogen) are such as would make it particularly effective in augmenting diffusion resistance were it present in any appreciable amount. In highly compressed air, argon (at 10 atms. it would be 9.4 per cent of 1 atm.) might very well increase the diffusion resistance and so contribute, at least in small measure, to the interference with CO_2 removal.

The experiments of Behnke and Yarbrough (1939) in which argon was used as a diluent for O_2 are particularly significant because they point to the importance of such physical properties as diffusion, and "respiratory resistance" in exposures to compressed gas mixtures. A comparison of the subjective and neuromuscular effects induced in experienced, emotionally stable, deep sea divers by their exposure to He-O_2, N_2-O_2 (air), and A-O_2 mixtures at pressures up to the equivalent of a 160 foot dive, showed that the He-O_2 mixture induced the least response; the response to the N_2-O_2 mixture was next in order of severity and the response to the A-O_2 mixture was most intense. The "greater stupefaction and neuromuscular impairment" induced by the argon mixture, as compared with that induced by the nitrogen (air), was said by the authors to be due to "the narcotic effect of argon" which "is greater than that of nitrogen at high pressures of 4 to 10 atmospheres." Now this order of effectiveness, helium-nitrogen-argon, of the gas mixtures in the induction of symptoms of intoxication, is exactly what one would expect on the basis of the physical properties of these gases and their influence on diffusion resistance and CO_2 removal. In any case the probability that the "narcotic action" of argon, nitrogen and helium may have been due to alterations in CO_2 removal have not been adequately ruled out.

The density and viscosity of a gas determines to a very large extent its facility and type of flow. The exact contribution of these properties to the involvement of CO_2 in the intoxication by compressed air or other gas mixtures under pressure,

aside from their influence on diffusion, is problematic, especially since viscosity of a gas may be diminished at increased pressure. In the normal lung at atmospheric pressure these properties would appear to be rather unimportant in pulmonary ventilation (Dean and Visscher, 1941). But with compression, especially where high pressures are attained, the density is distinctly altered and to such degree that a dismissal of this factor as entirely inconsequential is hardly justified without more factual evidence. Certainly if there is a flow of gas in the more terminal portions of the lung, the diameter of the smaller tubes (0.19 mm., Miller, 1937) and the possibility of their active constriction (Macklin, 1929) would enhance the importance of any change in the flow characteristics of the respired gas. Bayliss and Robertson (1939) localize the "viscance" of respired gas in the terminal bronchioles and at the entrance to the alveoli. This is supported by the anatomical findings of Baltisberger (1921) and Miller (1937) who described rings of muscular tissue of sphincters between the bronchioles and the alveoli in human lungs.

Behnke and Yarbrough (1939) were unable to detect any difference in resistance to gas flow of $He\text{-}O_2$, $N_2\text{-}O_2$ (air), or $A\text{-}O_2$ mixtures at atmospheric pressure, but elevation of the pressure progressively increased the resistance to flow so that at 4 atmospheres it was more than 100 per cent above the value for 1 atmosphere. This increase in resistance with increase in pressure is especially noteworthy because in actual respiration tests no difference in "respiratory resistance" could be felt by the subjects breathing these same gas mixtures either at atmospheric pressure or at a pressure of 4 atmospheres. At a pressure of 10 atmospheres, however, the subjects "were able to breathe argon-oxygen for a few minutes only because of the increased resistance to breathing and the narcotic action of argon." The report of Case and Haldane (1941b) on the increased resistance to breathing in highly compressed air also points to the practical importance of the viscosity and increased density of respired gas under conditions of compression.

If diffusion resistance and the resistance to mass movement because of increased gas density are greater in compressed air than in air at normal pressure they should, other things being constant, tend to maintain a supranormal alveolar CO_2 tension. The data of Hill and Greenwood (1906) and of Haldane and Priestley (1935) are of interest in this connection; these authors concluded that exposure to air at 75 pounds' pressure did not alter the pulmonary CO_2 and although Haldane and Priestley interpret the data as evidence of a constancy of alveolar CO_2 tension and the regulation of breathing "so as to keep the partial pressure of CO_2 steady," an examination of the Hill and Greenwood data as used by Haldane and Priestley (table 2) reveals two features relevant to the question of the effect of increased pressure on CO_2 removal—especially if the breathing were regulated as claimed.

The data show first, that with few exceptions the alveolar CO_2 tension even with a relatively small increase in air pressure was higher than that which could be accounted for simply by the CO_2 in the ambient air. Furthermore, this elevation of alveolar CO_2 tension could not have been caused by a rapid compres-

sional inflow because the rate of compression was very slow. Granting there is no increase in metabolism under increased air pressure, this elevation of alveolar CO_2 indicates a retention of CO_2. Under such conditions a new set of CO_2 diffusion gradients would be built up; the organism could continue to function at a higher CO_2 level and the subjective symptoms of compressed air viewed as CO_2 effects need not then become progressively more severe as the air pressure is maintained. Furthermore as Case and Haldane (1941b) have observed, high percentage of CO_2 at atmospheric pressure do not seem to have any cumulative action over prolonged periods of administration.

The second, and perhaps equally significant feature revealed by the data tabulated below, is the fact that the elevated alveolar CO_2 tension did not drop as the pressure was lowered, as it should have done if it simply represented the CO_2 of the ambient air. Even on return to 760 mm. Hg the alveolar CO_2 tension was still above the pre-compression value. This lag in the return to normal alveolar CO_2 tension perhaps is most logically explained as due to a lag in the post

TABLE 2

ATMOSPHERIC PRESSURE	ALVEOLAR CO_2-PERCENTAGE		ALVEOLAR CO_2 PRESSURE	
	Hill	Greenwood	Hill	Greenwood
mm. Hg			*mm. Hg*	*mm. Hg*
760	4.7	5.3	33.5	37.8
4,640	0.75	0.9	34.4	41.3
3,860	0.95	1.0	36.2	38.1
3,090	1.2	1.3	36.5	39.5
2,310	1.8	1.8	40.7	40.7
1,540	2.5	2.7	37.5	40.5
760	5.0	5.4	35.6	38.5

decompression removal of the CO_2 which had accumulated in the tissues during the exposure to increased pressure.

Reasons why the diminished severity of the subjective and neuromuscular reactions to compression by the use of the He-O_2 mixture does not constitute valid evidence that nitrogen acts as a narcotic have been presented above. To these there may now be added several others which involve the physical factors under discussion.

The results of substituting helium for nitrogen in a compression mixture cannot be safely considered simply as due to the absence of a direct or narcotic action of nitrogen unless such substitution introduces no new physical conditions which might at the same time alter the removal of CO_2. But obviously enough, the substitution of helium for nitrogen in the compression mixture does alter the physical factors of resistance to gas flow (Behnke and Yarbrough, 1939), of gas density, and of diffusion, all of which may influence CO_2 removal. The properties of helium are such as to facilitate the removal of CO_2 by diffusion and its use should therefore diminish the CO_2 effects on the organism. Dean and Visscher (1941) suggest that the faster rate of CO_2 diffusion in helium-oxygen mixture

than in air may be one argument for the use of helium therapeutically. The finding that the use of helium as a diluent for O_2 diminishes the subjective and neuromuscular effects of compression is, then, in accord with what one might expect if CO_2 were the causative agent and such finding therefore fails to provide substantiation for the "nitrogen narcosis" hypothesis.

The fact that while the substitution of helium for nitrogen diminishes the intoxicating effects it does not eliminate them (Case and Haldane, 1941) deserves particular emphasis in this connection. The report of Behnke and Yarbrough (1938) provides additional evidence of the failure of helium to eliminate the compressional effects of neuromuscular mechanisms. A condensed tabulation of the data derived by these investigators from experiments in which a skilled typist was subjected to compressed air and to compressed helium-oxygen mixtures is presented below in table 3. This shows that while the typing speed was reduced by 17.7 per cent when breathing the helium-oxygen mixture at a pressure equivalent to that of a 250 foot depth, it was reduced only by 5 per cent when breathing air at the same pressure. These results are interestingly interpreted by the authors who say, "Impaired judgment, a characteristic effect of high air pressure, is brought out by the fact that the typist realizing that he was making errors

TABLE 3

Pressure cond. Respiratory medium	Surface		200 feet depth		250 feet depth	
	Air	$He-O_2$	Air	$He-O_2$	Air	$He-O_2$
Words per min	63.2	69.0	53.0	63.0	60.0	55.8
Errors per stroke	0.0032	0.0052	0.0135	0.005	0.011	0.0057

while breathing helium slowed down his rate of copy." On the other hand, the fact that raising the pressure of the $He-O_2$ mixture to the pressure equivalent of a water depth of 250 feet distinctly slowed the rate of typing, indicates that $He-O_2$ at increased pressure does alter neuromuscular processes and subjective reactions. The failure of the substitution of helium for nitrogen to eliminate the intoxicating effects of compression constitutes further evidence for questioning the "nitrogen narcosis" hypothesis in compressed air intoxication.

If the intoxication which has been ascribed to "nitrogen narcosis" occurs even in the absence of nitrogen, some other explanation is obviously called for; in the case of the intoxication induced by the argon-oxygen mixture it was concluded that argon must have been the responsible agent and that therefore it also must possess narcotic properties (Behnke and Yarbrough, 1939); on similar grounds narcotic properties must also be delegated to helium. But the intoxicating influence of these gas mixtures may, as already pointed out, be more logically explained on the basis of an alteration in removal of CO_2. In any case the data at hand do not appear to warrant the conclusion that the intoxicating effects experienced when compressed in $He-O_2$, N_2-O_2 or $A-O_2$ mixtures are caused by a direct narcotic action of helium, nitrogen and argon on the organism.

There are several more points relating to the use of $He-O_2$ mixtures which

would appear to be worthy of brief mention. These concern the effects of shifting from one gas mixture to another while the pressure is maintained at a constant high level. In shifting from a He-O_2 mixture at high pressure to air at the same pressure, there would of course be no compressional inflow of gas into the lungs. One would expect therefore that the symptom onset of compressed air intoxication would be somewhat more delayed than in those cases where the increased air pressure had been attained by rapid compression. Although no definite experimental comparison of the time of symptom onset seems to have been carried out, Case and Haldane (1941b) report that on shifting from He-O_2 to air it takes several minutes for the subjective symptoms to develop. This delay might be interpreted in terms of the "nitrogen narcosis" hypothesis as the time lapse necessary for the narcotic action of nitrogen to become effective; but this delay is again well explained on the CO_2 theory, for in the absence of a compressional inflow the accumulation of CO_2 would be less rapid and the subjective effects of somewhat slower onset than in those situations where compressional inflow occurred.

But in spite of the short delay in symptom onset occasioned by the absence of compressional inflow the influence of CO_2 should nevertheless become rapidly manifest on shifting from He-O_2 to air at high pressure. The greater density of the air as compared with the He-O_2 mixture and the increased resistance to CO_2 diffusion attending such a shift would immediately begin to operate in slowing the CO_2 removal, or at least before the air had reached the ultimate respiratory epithelium; maximal effects could not be expected, however, until the alveoli had been washed free of He. On the other hand any direct narcotic action of N_2 could not take place until some time after the air had reached the alveoli and was present there in relatively high concentration. The effects of CO_2 retention would, therefore, be expected to be earlier in onset than those of any narcotic action of N_2; but in either case a short delay such as that described by Case and Haldane would of necessity be involved.

If, as some authors have insisted, the onset of subjective symptoms of compressed air intoxication is "immediate" some other explanation than either "nitrogen narcosis" or increased CO_2 will have to be sought. However, if by the term "immediate" a lapse of a minute or so is meant, such immediacy of symptom onset is more readily explained on the basis of CO_2 retention than on that of the "nitrogen narcosis" hypothesis, especially where compressional inflow occurs.

The reports of Swindle (1937) and of End (1938) introduce another suggestion concerning the action of CO_2 in compressed air. End (1938) states that "agglutination of erythrocytes appears to be the primary disturbance in compressed air illness and that bubble formation may be looked upon as a serious complicating factor." Swindle has maintained that carbonic acid is probably the principal known agglutination factor normally present in the body and that this, working in conjunction with some unknown factor, promotes intravascular agglutination. On this basis End has attempted to diminish the effects of compressed air by alkalinization through the ingestion of sodium bicarbonate. To date there appears to be no further evidence in support of these contentions and it would ap-

pear unlikely that agglutination contributes to the occurrence of the subjective symptoms of compressed air intoxication.

In a problem such as this of compressed air intoxication where the variables are exceedingly difficult, if not impossible to control completely, and where the evidence indicates a very high probability of an indirect, if not direct, involvement of several etiological factors, it would appear unwise to insist that the solution lies in some single key factor. Certainly the available data do show that the presence of nitrogen constitutes an important contributory factor to the occurrence of compressed air intoxication; but an analysis of those data reveals no evidence sufficiently substantial to warrant the conclusion, either that nitrogen itself has a direct narcotic action, or that "nitrogen narcosis" is the cause of compressed air intoxication. On the other hand there is an imposing array of evidence which points to CO_2 as an exceedingly important, if not the prime, etiological agent, not only of compressed air intoxication but also of argon and helium "narcosis." The whole question of "nitrogen narcosis" and CO_2 influence in compressional intoxication calls, however, for further critical experimental investigation.

The present data make it appear highly improbable that either the CO_2 influence, or "nitrogen narcosis" if such there be, operates alone. Increased O_2 tension, especially when present in excess of that equivalent to one atmosphere, must also contribute to the response to highly compressed air, either by modifying the reaction of the organism to CO_2 or perhaps by a more direct effect on the cells themselves.

Psychological factors likewise cannot be completely dismissed. The fact that so much attention in the selection of the personnel for deep diving is directed to psychological and emotional stability is, in final analysis, simply a recognition that the physico-chemical adjustment of the so-called unstable individual, when exposed to conditions of stress, is peculiarly susceptible to the superimposition of the adverse changes inherent in an exposure to abnormal environments. Such selection is a general admission that psychological factors do determine in large part an individual's reactions to pressure conditions such as those met in deep diving. Because they are psychological renders them no less real and they may frequently be more menacing, than those one likes to think of as strictly physiological and with which they are inextricably interwoven.

III. Effects of oxygen tensions in excess of one atmosphere, as induced by pure oxygen, hyperoxygenated or normal air at high pressure. It is only to be expected that some of the changes induced by O_2 enriched air or pure O_2 at normal barometric pressure would also be seen under conditions where the organism is exposed to O_2 tensions in excess of 760 mm. Hg, which conditions are inclusively referred to below as those of O_2 at high pressure (OHP). But there are some added and distinct effects induced by exposure to OHP, not observed at lower O_2 tensions, which have a somewhat more involved etiology. For these reasons the effects of O_2 at high pressures appear to warrant consideration as a special phase of a more inclusive topic, although the line of demarcation is not sharp and is admittedly an artificial one.

The first investigation of the effects of OHP was that carried out by Bert (1878) as a part of his extensive study of the reactions to breathing air and various gas mixtures at pressures both above and below that of the normal barometric reading. The experiments of Boyle (1670) and of Hoppe (1857) had clearly indicated that gas emboli would in all probability be an important etiological factor in decompression illness but it was Bert's animal experimentation which first demonstrated unequivocally that the real cause of this illness was the formation of N_2 bubbles in the blood and body fluids on decompression. His experiments also showed that by breathing a gas mixture of high O_2 and low N_2 content this danger of bubble formation during decompression was very appreciably diminished. Thus he had anticipated by about a quarter of a century von Schrötter's suggestion (1906) that breathing OHP for five minutes to wash the tissues of dissolved nitrogen before decompression was begun, might facilitate safe return to atmospheric pressure. But of all his numerous observations, the one which seems to have impressed Bert most was the finding that OHP acted like a poison, and he concluded that OHP was toxic to every living thing.

1. *Convulsive Seizures.* The most striking feature of the toxic action of OHP which Bert observed was the occurrence of convulsive seizures. These he described as similar to those induced by strychnine or phenol poisoning. After their removal from the pressure chamber, dogs were observed to be in a state of tonic rigidity. He concluded that these convulsive attacks were due to the action of the high O_2 tension on the C.N.S.—a presumption which he maintained was substantiated by his observation that chloroform inhalation arrested the attacks and that the influence of OHP on peripheral tissues was not such as could cause the attacks.

Interestingly enough, many of the seizures which he observed appeared during or just after quite rapid decompression, so that some of these attacks must have been complicated by decompression phenomena. His results must have been further complicated by his failure adequately to rule out the influence of CO_2 in the respired gas, and by his use of highly compressed air. (See section on etiology below.)

The susceptibility to the convulsant action of OHP, Bert found, varied in different animals, e.g., small birds were convulsed by O_2 at pressures of three atmospheres or an equivalent of air at fifteen atmospheres of air pressure, but dogs were more resistant and required about four atmospheres (380 per cent of an atmosphere). If, however, the exposures were prolonged, convulsive seizures occurred even at lower pressures. Thus Bert recognized three important determinants in the precipitation of the convulsive attacks; the individual susceptibility of the animal; the intensity of O_2 pressure; and the duration of the exposure. Lehmann (1884) disputed Bert's interpretation and maintained the convulsions were modified asphyxial convulsions.

Bert's early observations find confirmation in the reports of many subsequent investigators. Thompson (1889) placed pigeons and a monkey in a pressure chamber and raised the pressure to 30 pounds (gauge) by the addition of O_2 (i.e., an environment equivalent to 2.2 atmospheres of pure O_2). The pigeons became

drowsy and while the monkey was at first playful it gradually became dyspneic and the respiratory rate rose from 35 to 70 per minute. Raising the pressure to 35 pounds caused some slight convulsions in the monkey, but they disappeared on decompression. There was no evacuation of urine or feces during the attacks. In other experiments Thompson placed a guinea pig, a dog, and an alligator in the chamber; the dog had a convulsion in 15 minutes at a gauge pressure of 60 pounds (4.2 atmospheres of O_2). The pressure was then lowered to 45 pounds and the animals appeared normal. After 75 minutes of exposure at this pressure and a subsequent slow decompression to normal pressure the alligator was still unaffected, but the dog and guinea pig both died in convulsions. "This experiment, with several others," Thompson says, "shows that the higher animals are sooner affected by pressure than the lower. The monkey was asphyxiated before the pigeons, the dog before the guinea pig."

The absence of any apparent effect in the alligator on the one hand and the lethal action on the guinea pig and the dog on the other, suggests that cold-blooded animals are somewhat more resistant to OHP than are warm-blooded. This would seem to be borne out by the finding of Cleveland (1925) that some frogs survive O_2 at pressures of 3.5 atmospheres for 65 hours, which is in accord with the reports regarding the effects of O_2 at atmospheric pressure on cold-blooded animals referred to in section I.

Thompson, like Bert, also described post decompressional effects. Three pigeons were subjected to O_2 at a pressure of 40 pounds (gauge) for 90 minutes. Only one of these was convulsed and on removal from the chamber it remained for some time with the muscles in a curious condition of rigidity and contracture; all attempts at moving it threw it into violent convulsions. The bird lay on its back for four days with neck and legs strongly flexed. Thompson thought that these peculiar symptoms may have been due to the pressure affecting the surface of the brain unduly through an opening in the skull which had previously been made for other experimental purposes, rather than to any influence of oxygen. The other two pigeons survived and were normal.

Thompson observed further that air pressure of 8 atmospheres caused convulsions in a dog on its first exposure. The next day the same animal exposed a second time was convulsed by O_2 at 5 atmospheres; 6.3 atmospheres caused exceedingly violent convulsions. It was also found that whereas after decompression from 8 atmospheres of air pressure the animal was normal, after decompression from O_2 at 6.3 atmospheres the animal had tremors, inco-ordination, salivation, staring eyes, and jerky dyspneic respiration, but there were no rales in the chest. Ether was given to control the convulsions which continued for some time and the animal survived.

Smith (1899) made a somewhat more extended study of the effects of OHP and noted that mice, rats, guinea pigs, small birds and pigeons responded to OHP in a manner essentially similar to that described by Bert. The occurrence of convulsive seizures while the animals were still under pressure was, however, more commonly observed. Restlessness, dyspnea, and minor temporary muscle spasms frequently preceded the convulsive attacks. Smith reasoned that if

OHP were toxic to the C.N.S., it should also cause damage to those tissues, particularly the lung, through which it had to pass on its way to the C.N.S. His post mortem examinations of the exposed animals revealed very distinct and often extensive lung damage, thus verifying his contention. It was also found that the tension of O_2 required to elicit the convulsive reaction was much higher than that required to produce the pulmonary damage and that when the lungs were thus damaged the tension required to produce convulsions was higher than when the lungs were normal.

Hill and Macleod (1903c) confirmed Smith's experimental results but their animals were somewhat more resistant to the toxic action of OHP. Smith had reported that O_2 at a pressure of 1.8 atmospheres caused death in about 24 hours and that O_2 at 3 atmospheres produced pulmonary inflammation in about 5 hours, whereas Hill and Macleod observed no symptomatic changes in a mouse after 6 hours of exposure to O_2 at 3 atmospheres. One animal survived 9 hours' exposure to O_2 at 4 atmospheres; cleaning movements, salivation, and jerky deep respiration preceded the convulsive attack which was followed by coma. Death, it was found, might occur even in the absence of convulsions, for some rats died after becoming simply dyspneic and comatose. At O_2 pressures of 3 to 3.5 atmospheres no convulsions were observed, but at 4 to 5 atmospheres they commonly were seen in mice, rats, rabbits and cats. Exposures of mice and birds to O_2 pressures of from 6 to 25 atmospheres quickly caused intense dyspnea and coma, but no convulsions; O_2 at from 50 to 70 atmospheres instantly threw mice into convulsions resembling those of acute asphyxia and death rapidly followed.

It was also noted that animals sometimes showed marked reflex hyperexcitability after decompression and occasionally violent tetanic spasms were evoked by handling the animals—an observation which had been made previously by Thompson (1889) and Bert (1878), and more recently confirmed by Ozorio de Almeida (1934) and the reviewer (1940, unpublished data). No convulsions were observed by Hill and Macleod in compressed air at pressures as high as twelve atmospheres during compression; this the authors thought was because under these conditions "the process of intoxication was too gradual."

Ham and Hill (1905) found that cats were convulsed in six minutes by O_2 at 50 pounds' pressure and in eighty minutes by O_2 at 23 pounds. There was no relationship between the size of the animal and the time of onset of convulsions. Because of the danger of O_2 convulsions these authors believed that it was unsafe to use von Schrötter's method of decompressing divers in O_2 pressures of 50 pounds and upwards. The authors claimed also that "any diving apparatus fitted with an oxygen cylinder, in place of air-pump and tube, is obviously too dangerous to use for many minutes at pressures over 25 pounds and should not be used for more than thirty minutes at that pressure." Some years later, however, Hill's opinion concerning the danger of O_2 was changed (Twort and Hill, 1912) and he recommended the use of O_2 under pressure as an aid in prevention of caisson sickness (see OHP in decompression, below).

Bean (1931) observed that pure O_2 at slightly over 3 atmospheres caused convulsive attacks in dogs anesthetized with urethane. Phillips (1931) found that exposure to O_2 at pressures of 45 pounds quickly leads to convulsions in animals.

In mice and rats the convulsive period was preceded by extensive washing operations which later changed into running convulsions; after a few seconds these were usually followed by a period of inactivity. When the pressure was lowered, convulsions were again observed, even in some animals which had not been convulsed while under the increased pressure. In O_2 at pressures below 45 pounds animals were found to be quite free from convulsions but in prolonged exposures they seemed to become stuporous.

The observation that convulsive seizures are not infrequently precipitated during decompression from high oxygen pressure calls attention to the possibility that O_2 emboli might be the responsible agent, especially since O_2 bubbles have been found in the blood of animals rapidly decompressed from OHP (Hill and Macleod, 1903c; Dorello and Rowinski, 1938). Hill and Macleod (1903c) were of the opinion that those convulsions observed in their own experiments during decompression from high O_2 pressure were embolic effects. Convulsions which occurred during rapid decompression from compressed air were soon followed by paralysis but those occurring in decompression from high O_2 pressures continued to be excited because, as the authors suggested, the O_2 set free maintained the life of the tissues.

Hill (1912) further maintained that "The convulsions which Bert details as occurring in dogs are clearly decompression results, and due to the effervescence of oxygen gas in the central nervous system. The convulsions which occur during compression are due to the high tension of the oxygen in solution in the tissue lymph. They occur by no means constantly, but only in certain individuals and under certain conditions. Often dyspnoea, coma, and paralysis come on without any marked stage of exaltation. There is one sign of excitement which is almost always present in mice, and that is rapid cleaning movements of the face. The convulsions seem never to occur when the O_2 tension is below 300 per cent atmospheres, or above 600 per cent atmospheres, excepting the instantaneous convulsions which precede the death of animals exposed to enormous pressures such as +60 to 70 atmospheres. We may assume that with pressures below 300 per cent atmospheres O_2 the amount of gas in solution is not sufficient to excite; that with pressure above 600 per cent atmospheres O_2 the inflammation of the lungs causes the collapse of the animal."

The presence of O_2 bubbles in the blood, however, does not necessarily result in convulsions. Dorello and Rowinski (1938) found that O_2 bubbles which formed in the mesenteric blood vessels of guinea pigs on rapid decompression from a 20 minute exposure to O_2 at 5 or 6 atmospheres caused no untoward symptoms and disappeared in from 2 to 4 minutes or less; recovery was complete. Human subjects exposed to O_2 at from 3 to 4 atmospheres for 30 to 40 minutes also withstood rapid decompression without showing any subjective or objective symptoms.

There is substantial evidence that those reactions precipitated by decompression from OHP are attributable to factors other than that of O_2 bubble formation. Ham and Hill (1905) in testing von Schrötter's suggestion that divers exposed to compressed air should wash out the nitrogen dissolved in their tissues by breathing pure O_2 for 5 minutes before decompression, found that experimental animals were intensely convulsed by rapid decompression following a five minute ex-

posure to O_2 at a pressure of 20 atmospheres, yet an examination of the blood showed surprisingly few bubbles. Further evidence that bubble formation is not the sole, or even the chief cause of these decompression convulsions is the difficulty which has frequently been experienced in safely returning dogs to atmospheric pressure even where O_2 bubble formation has been eliminated by very slow decompression after exposures to OHP for several hours (Bean and Rottschafer, 1938). Similarly the reviewer has found that convulsive seizures commonly occurred in unanesthetized rats during very slow decompression from relatively short exposures to OHP; these again cannot be explained as due to bubble formation. Some rats are peculiarly susceptible to audiogenic convulsions so that the noise of escaping gas during decompression may contribute to the precipitation of the decompressional convulsions.

The responses of isolated smooth muscle (Bean and Bohr, 1940) indicate that decompression from OHP does not immediately initiate recovery, indeed decompression appears at times actually to cause a temporary exacerbation of the effects induced by the OHP. It may be that this decompressional effect, which cannot be explained either by bubble formation or lung damage, is a response caused by a shift in function of enzyme mechanisms within the tissues. The situation would then be essentially similar to that proposed above as a possible explanation for the failure of animals adequately to readjust themselves to normal atmospheres after having been "acclimatized" to O_2 rich atmospheres at normal pressure.

Shilling and Adams (1933) described experiments on guinea pigs, rabbits and cats in which successive O_2 convulsions, characterized by extensive rigidity of the entire body, occurred at short intervals; these seizures later became continuous and ended in death. No attacks occurred in a two hour exposure to O_2 at gauge pressures of 35 pounds or below, but all species developed convulsions within two hours at pressures of 55 or 60 pounds. Considerable individual variation in the susceptibility to O_2 convulsions was noted. Rabbits were more susceptible than guinea pigs and rats; cats were relatively quite resistant. The lung damage induced by the O_2 and the occurrence of convulsions were not causally related. These authors believed their results "constitute a warning against the uncontrolled use of pure oxygen for rapid decompression of divers and in the submarine 'lung' when escaping from great depths." Ozorio de Almeida (1934) likewise found both convulsive responses and pulmonary pathology occur in animals as a result of exposure to OHP.

Dionessow et al. (1934) in accord with other observers, noted convulsions in warm blooded animals exposed to O_2 at pressures up to 8 atmospheres and remarked that there were wide individual differences in susceptibility, but contrary to the reports of others (Hill and Macleod, 1903c). Dionessow et al. found frogs were immune to the convulsant action of OHP. The authors maintained that the susceptibility in the higher animal forms is directly related to the greater C.N.S. development. Iwanow et al. (1934) reported that decerebration and removal of the optic thalamus prevented the convulsive seizures of O_2 poisoning as did also certain types of anesthesia.

Morphine-urethane as used in routine anesthesia however does not prevent O_2

convulsions, although with heavy doses of such anesthetic the severity of the attacks is diminished (Bean, 1929, 1931). Shilling and Adams (1933) reported that nembutal and veronal prevent the convulsions but not the lung damage of O_2 poisoning. In dogs anesthetized with sodium diethylbarbiturate, Behnke, Shaw, Shilling, Thomson and Messer (1934) observed modified convulsive seizures, characterized by violent spasms confined to the muscles of the head, neck and thorax, and accompanied by a pronounced respiratory reaction. Bert (1878) found ether anesthesia relieved O_2 convulsions.

Pure O_2 at atmospheric pressure tends to diminish the depth of anesthesia (Davidson, 1925); and when the O_2 pressure is increased to several atmospheres the release from anesthesia appears to be even more rapid and pronounced (Bean, 1931). Such an effect introduces the complicating possibility that reactions interpreted as convulsive seizures in anesthetized animals may in actuality represent a struggle of the animal due to lowered anesthesia.

In order to eliminate the complicating influence of OHP on chemical anesthesia, Bean and Rottschafer (1937, 1938), unaware of the report of Iwanow et al. (1934) resorted to decerebration and decortication as a means of anesthesia for experiments to be carried out with OHP. Contrary to the observations of Iwanow et al. it was found that severe convulsive attacks involving clonic and tonic features occurred in both the decorticate and decerebrate animals. The onset of such attacks was usually heralded by a distinct twitching of the external nares, lips, or some other facial muscle. Alterations in respiration always preceded the convulsive seizures. These respiratory changes were usually typified by a gradually developing hyperpnea which became jerky, irregular and panting in nature; later there developed a deepening and slowing with pronounced dyspnea. The expiratory effort became progressively more violent and assumed the appearance of a tonic convulsive expiration involving the greater part of the body musculature and was broken by rapid gasping inspirations. The convulsive response spread also to the inspiratory phase and breathing was frequently stopped temporarily; clonic limb movements unrelated to the respiratory cycle merged into a tonic reaction and the animal attempted to assume an opisthotonic position. Dilatation of the pupils, exophthalmos, excessive salivation, emesis, relaxation of sphincters with resulting defecation and urination were commonly observed during the seizures. It was also shown that the functional activities of the carotid sinuses and bodies, as well as of the aortic arch and aortic body and pulmonary nervous mechanisms are not essential to the occurrence of the convulsive seizures of O_2 poisoning. Considerable individual variation was found in the susceptibility of decerebrate animals to the convulsant action of OHP just as there is in chemically anesthetized and non-anesthetized animals.

Preceding the convulsive attacks in O_2 at about 5 atmospheres, unanesthetized rats appear to experience various paresthesias. This is suggested by the peculiar behaviour of the animals; in addition to the twitching of facial muscles, the restlessness and face washing described by several investigators, the animals shake themselves intermittently and vigorously as though drying their fur and subject their genitalia to industrious cleansing processes. Male rats which have experienced O_2 convulsions almost invariably were found to have a very adherent

cast of hardened ejaculate of waxy consistency which filled the prepuce and urethra. In rats so affected by OHP as to render cleaning themselves impossible this cast unless manually removed, remained adherent for days, completely plugging the urethra. It is important, therefore, that male rats which have experienced O_2 convulsions be examined and the urethral cast removed if the animal is to be used for subsequent study (Bean, 1941).

Ozorio de Almeida (1934) reported that the susceptibility to the toxic action of OHP was increased by successive exposures; this sensitization, it was claimed, applied not only to the convulsive response but also to the pathology induced in the lung. This sensitization was observed even in animals exposed for periods too short to induce any obvious toxic symptoms and those animals which on removal from the OHP appeared to be entirely normal were convulsed in a much shorter time when exposed again after a 24 hour interval, than were those not previously exposed. The increased sensitivity to OHP persisted for three or four days after an exposure, then gradually disappeared. This persistency of an increased sensitivity indicates that the animals do not completely or immediately recover on decompression. Further evidence that recovery is not complete even several days after decompression is the retention of a hyperexcitability and the change from a docile to a combative attitude (Ozorio de Almeida, 1934; Bean and Siegfried, 1943). Young animals were found by Ozorio de Almeida to be more resistant to the convulsant effect of OHP than adults, and starved animals withstood the OHP better than the well-fed. The observation that young animals are more resistant to the toxic action of OHP than old finds confirmation in the report of Prikladowizki (1936).

Hederer and Andre (1940) summarize the progressive responses which they observed in a rabbit exposed to O_2 at a pressure of 8 atmospheres absolute as follows:

DURATION OF EXPOSURE	OUTSTANDING SYMPTOMS
minutes	
1–5	Erection of ears with dilatation and redness of the blood vessels
5–10	Spasm of superciliary, orbicular and masseter muscles; trembling of the lips; protrusion of the eyeballs
10–15	Agitation and restlessness, spasmodic trembling of the limbs and trunk; partial or general rigidity; emission of urine
15–18	*Convulsive epileptiform crisis* with violent torsion of the trunk, somersaults, movements of the distal portion of the feet, revulsion of the eyeballs, hyper-extension of the head
18–22	Four more crises resembling combined general convulsions to the phase of tetanic rigidity
22–28	Succession of three severe crises as of the preceding type with muscular jerks localized (lips, masseters, limbs) *in muscle groups commonly employed*
29–32	Animal "affalé", motionless, slowed respiration (25–30) some clonic muscular shaking
32–36	Coma with superficial respiration and arrhythmia, death

The lethal and the convulsive threshold for animals in terms of duration of exposure and O_2 pressure and that which was considered as the threshold for safety in man have been graphically represented by Hederer and Andre (1940) and are redrawn below.

Hederer and Andre maintain that the acute intoxication by O_2 follows the general law of mass action; that this acute intoxication which they designate as the "Paul Bert Effect" is reversible, but that the "Lorraine Smith Effect" (lung pathology) is an irreversible process. Both effects are thought to be operative in OHP and cannot easily be separated by the use of certain degrees of pressure. These authors, like Ozorio de Almeida (1934) and Dionessow et al. (1934), found that animals which had suffered one exposure to OHP were more susceptible to the toxic action in subsequent exposures, a result which again implies there are

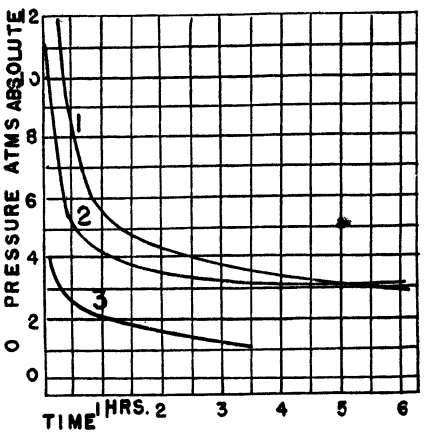

Fig. 1. Curve *1* represents the threshold for lethal intoxication; curve *2*, threshold for convulsive intoxication; curve *3*, the safe threshold for man in diving and salvage apparatus. (Redrawn after Hederer and Andre, Acad. Med. 123: 294, 1940.)

residual effects of exposure to OHP and that recovery is not complete on decompression.

Their results also confirm the finding of Ozorio de Almeida (1934), as do those of Campbell (1937a), that starvation plays a protective rôle against the occurrence of O_2 convulsions. Carbon dioxide, added to the OHP in small amounts, was found precipitates convulsive seizures, thus emphasizing the importance of CO_2 in O_2 poisoning. Strychnine, it was found, accentuates the O_2 poisoning but barbiturates exercise some antagonistic action, retarding, diminishing, and even stopping the convulsions.

Williams and Beecher (1944) describe various stages in the development of poisoning by OHP in Drosophila analogous to the motor disturbances and convulsions induced in mammals by OHP. An initial period of excitation is followed by loss of both reflex wing movement and initiation of flight; stiffening of the legs ensues and there is a loss of spontaneous movement and reflex excitability. These observations are somewhat at variance with the report of Bert that while

beetles and similar forms of life are killed by OHP they do not show any excitation or reaction analogous to convulsions.

The observation by these investigators that CO_2 enhances the toxic action of OHP on those forms of life devoid of hemoglobin is particularly noteworthy and is in accord with a similar enhancement which occurs in higher forms (Gesell, 1923; Hill, 1933; Shaw et al., 1934; Hederer and Andre, 1940, and others). Twenty-four hours after a 1 hour exposure to O_2 at a pressure of 5 atmospheres, recovery, judging from wing beat frequencies, was apparently complete but there were residual effects following exposures of 2 hours' duration. The inability of Drosophila to fly in air compressed to 10 atmospheres as observed by Case and Haldane (1941) may have been due in part then to the effects of OHP in addition to the increased density of the air which those authors implied may have been the cause.

Valenzuela (1887) appears to be the first to have subjected man to O_2 at pressures slightly greater than one atmosphere for therapeutic purposes, and Boycott, Damant and Haldane (1908) breathed O_2 at a pressure of 1.7 atmospheres for a few minutes without experiencing any untoward reactions. But Bornstein (Bornstein and Stroink, 1912) is to be credited with being the first investigator willing to risk exposing himself to OHP to a point of eliciting subjective and neuro-muscular responses. He experienced muscular cramps after a 50 minute exposure in O_2 at a pressure of 3 atmospheres. The observations of Bornstein and Stroink concerning the convulsive responses and pathologic lung changes induced in dogs and rats by OHP, conform with those described by the earlier investigators.

Thompson (1935) reported that in 1933 two British naval officers using themselves as experimental subjects found that breathing O_2 at a pressure of 45 pounds caused symptoms of convulsions in 16 and 13 minutes. In one, violent twitching of the face occurred but this was relieved by shifting to breathing air; in another there was twitching of the lips but in spite of shifting to air this passed into clonic convulsions and a loss of consciousness.

Behnke, Johnson, Poppen and Motley (1935) found that one of their human subjects after breathing O_2 at four atmospheres for 43 minutes experienced a transient syncope associated with blanching of the face, sweating of the hands, absence of radial pulse and a drop in blood pressure. Inhalation of air brought about what appeared to be an immediate and complete recovery. Another subject in a similar exposure felt well for 43 minutes; no significant changes occurred in the pulse rate, the blood pressure, the respiratory rate or minute volume, but during the 44th minute a temporary twitching of the left eyebrow was observed. The subject then uttered a short cry and developed a convulsion characterized in the beginning by violent tonic movements, and then by clonic contractions of the muscles of the head, trunk and extremities. Cyanosis did not occur and sphincter control was maintained. With subsidence of the convulsive movements the subject was in a stuporous condition for about 13 minutes. During this period the face turned an ashen gray color, beads of perspiration appeared on the forehead and breathing became stertorous. When he regained consciousness

20 minutes after the onset of the convulsion, the subject thought he had fallen asleep. Recovery was said to have been complete.

In another series of experiments Behnke, Forbes and Motley (1936) found that during the first three hours of exposure of a man to O_2 at a pressure of 3 atmospheres, there was a moderate facial pallor, dilatation of the pupils, impairment of visual acuity, and a rise in diastolic blood pressure, but no "distressing" symptoms. A period of threatened attack came on abruptly during the fourth hour and was characterized by dizziness, nausea, and a feeling of impending collapse, an increase in pulse rate, a rise in both systolic and diastolic blood pressure of 15 to 20 mm. Hg, rapid contraction of the visual field to a 10° circle, and failure in visual acuity for form and color. Left temporal hemianopsia and unequal dilatation of pupils was observed in one subject. Consciousness was retained, but the subjects looked dazed and partially stupefied. Recovery was gradual and took place within about 20 to 60 minutes after removal from OHP. The persistence of effects for such a length of time after decompression illustrates further that the effects of exposure to OHP are not immediately reversible on decompression, as has been claimed by Shaw, Behnke and Messer (1934).

TABLE 4

DEPTH OF H_2O	MINUTES	DEPTH OF H_2O	MINUTES
100	60	200	6
120	20	250	4
150	8	300	3

The British Admiralty Committee observed that men sitting in a chamber of O_2 at a pressure of 3 atmospheres showed no abnormal symptoms, but that in diving trials where the men were at work, O_2 pressures of even less than 2 atmospheres caused abnormal behavior and loss of memory (Haldane and Priestley, 1935). These effects the authors say "were strongly suggestive of some influence on the brain similar to that arising from low oxygen." The more pronounced response in actual diving trials as compared with those observed in the compression chamber tests, finds confirmation in observations of Behnke and Yarbrough (1938) who, as has been mentioned above in connection with "nitrogen narcosis," found that the response to compressed air in actual diving was much more severe than that elicited by the same air pressure in an experimental compression chamber. Jenkinson (1940) agreeing with the data of Damant states that it is unlikely that convulsions will appear at various pressure in less than the time presented in table 4. The only premonition was said to be a twitching of face muscles and paresthesia in the extremities.

Haldane (1941) reported that in O_2 at 7 atmospheres convulsions came on with little warning, but that there was a slight feeling of anxiety. The clonic seizures were very violent and caused a back injury which was painful for more than a year. These seizures lasted for about two minutes and were followed by flaccidity. That author says: "I wake up into a state of extreme terror in which I

may make futile attempts to escape from the steel chamber, whereas, like others, I am quite calm on recovery from carbon dioxide nitrogen narcosis.... At 7 atmospheres five minutes' exposure is about the limit tolerated. It is obvious that convulsions of this sort would be fatal if they occurred while a man was wearing an escape apparatus under water." An inadvertent exposure of the same subject (J.B.S.H.) to O_2 at 10 atmospheres also resulted in a severe convulsion (Case and Haldane, 1941b). The observation of making futile attempts to escape from the chamber is of particular interest for it has been reported that some divers at great depth have been so affected as to attempt to unscrew the face plate of their diving helmet—an aberration which some would attribute to nitrogen effects.

2. *Breathing.* Although Bert claimed that compressed air caused a change in position of the diaphragm and an increased thoracic capacity because of mechanical factors, he apparently considered that such changes were not of any determining significance in the response of animals to OHP. He recognized, however, that changes in breathing constituted a prominent feature of the convulsive attacks induced by O_2 at pressures of about 3 atmospheres. During these attacks the breathing was observed to be very deep and precipitous and in successive attacks it became slower and sometimes completely stopped. On the other hand, he had also observed that sometimes the respiratory rate was as high as 50 to 70 per minute, especially in birds. Lehmann (1884) maintained that the response of mice and birds to OHP was essentially respiratory, the dyspnea, characterized by slowed deepened breathing became convulsive and was asphyxial in type.

Thompson (1889) reported that although breathing in O_2 at atmospheric pressure was not materially different from that in air, in O_2 at a pressure of 2 atmospheres, respiration became jerky and dyspneic. The frequency of breathing in animals with complete collapse of one lung was found to be reduced both by compressed air and compressed O_2 but he thought that under such conditions the mechanical effects of the increased pressure added greatly to the distress of the animal.

Smith (1899) observed in his experimental animals exposed to OHP that embarrassment of respiration and dyspnea set in some time before death. Hill and Macleod (1903c) considered "gaping" and jerky, deep respiration as symptoms which precede the convulsions of vertebrates exposed to O_2 at pressures of from 4 to 5 atmospheres and that dyspnea precedes the coma induced by exposure to O_2 at pressures of from 6 to 25 atmospheres. Lehmann (1884) and Hill (1906) stated that OHP kills as if by asphyxia. Dautrebande and Haldane (1921) reported that breathing O_2, particularly at increased barometric pressure, increases breathing. Gesell (1923) observed dyspnea in rats exposed to OHP, and finding also that the respiratory response to CO_2 was more pronounced under such conditions than in air at normal pressure, suggested that the effects of OHP on breathing warranted closer study. That such a study was in order was indicated also by the limited data and the fact that practically all of them had been derived simply from observations made through windows in the pressure chamber walls. The problem obviously called for newer methods of investigation.

It has been argued by some that to obtain reliable data the pressure chamber in such investigations should be such as to admit the operator and observer himself; that argument is, of course, quite valid for investigations on man, especially when subjective reactions are concerned. On the other hand, the presence of the observer within the chamber introduces a very distinct disadvantage and in some cases a new source of error, the importance of which has not always been recognized. Where the observer is exposed to the increased pressure, whether it be air or O_2, he too becomes an experimental animal and the data obtained under such conditions may completely lose their objectivity or be seriously distorted. This point has been emphasized (Bean and Rottschafer, 1938) and finds some of its best support in the observations of those investigators (Behnke et al., 1934) who have advocated the exposure of the observer to the increased pressure along with the experimental animal. For example, it has been found (Behnke, Thomson and Motley, 1935) in an observer exposed to increased air pressure of from 3 to 4 atmospheres that "the palpation of the pulse of another worker was accomplished only with extreme difficulty" and that there was "partial stupefaction." All of the entire group of laboratory workers so exposed were reported to be affected emotionally, mentally and neuromuscularly, to such a degree that normal conduct could be maintained only with a great degree of self-control, that the mental activity was slowed and the responses to visual, auditory, olfactory and tactile reception were delayed; errors were frequently made in arithmetical calculations and in the recording of data.

The findings of Case and Haldane (1941b) offer further evidence that when possible the observer should not be subjected to the same conditions of pressure as the animal to be studied. These authors state that in air at increased pressure "It is quite imperative that no great trust should be placed in human intelligence. . . ." One of their subjects who was a "responsible scientist at atmospheric pressure" was detected "cheating" in a manual dexterity test while under pressure. The effects described by Case and Haldane have been attributed to increased nitrogen tensions, but increased tension of O_2 may also deprive the investigator of his objectivity; a man, who, after breathing OHP for 43 minutes ". . . suddenly experienced a transient syncope associated with a blanching of the face, sweating of the hands, and absence of the radial pulse" (Behnke et al., 1934) would seem to be in no condition to make objective observations. The report of Barcroft (1938) concerning subjective effects of CO_2 is also of interest in this connection.

It would appear from the literature, then, that except where the observer's own subjective responses are under investigation, the data obtained through an operator who is himself subjected to the same pressure as the experimental animal are very probably highly coloured by his own psychological, neuromuscular and mental responses and should be accepted only with considerable reservation. It is of paramount importance, therefore, that, wherever the investigations on high O_2 or air pressure permit, the regulation of the experiment and observations should be made by operators from without the compression chamber.

Many of the disadvantages encountered in the use of either the older methods

of simple visual observations or in those methods necessitating the presence of the operator within the chamber have been circumvented by the use of apparatus (Bean, 1929, 1931) which permits the continuous graphic recording of breathing and respiratory minute volume, blood pressure, heart rate, volume flow of blood, and blood acidity changes. Such apparatus also provides means of observing blood color changes, of sampling the continuously circulating blood, and of making intravenous injections while the animal is maintained at high pressure, yet the animal remains throughout, as completely under control as it would were the operator with it inside the chamber. Graphic recordings of respiration obtained by these methods showed that exposure to O_2 of from 3 to 5 atmospheres caused a gradual increase in respiratory minute volume. Usually both increased rate and depth of breathing were evident, but very commonly the increased depth was the more prominent change. Not infrequently there occurred an initial slowing of breathing immediately after raising the pressure. In the shorter exposures (about one hour duration) the increased respiratory minute volume induced by the OHP was reversed by decompression to atmospheric pressure. The experiments of Shilling and Adams (1933) likewise emphasize the respiratory response to OHP. They found that in guinea pigs the respiratory rate was increased during the early minutes of exposure to increased oxygen tension, then slowed somewhat but the dyspnea just preceding the convulsions was in all cases quite marked.

In decerebrate animals exposed for more prolonged periods to OHP the convulsive seizures were usually preceded by a relatively sudden alteration in the hyperpnea induced by OHP (Bean and Rottschafer, 1937, 1938). These alterations showed considerable individual variation, but as a rule there occurred a secondary slowing of the respiratory frequency as the exposure was continued. Each rapid gasping inspiration was immediately followed by forcible expiration, rapid in the early part of the phase, but slower as the expiratory force was mobilized from an involvement of practically the whole body musculature in a tonically spasmodic expiration. A shift from OHP to air at the same pressure very commonly was followed by a partial return toward the normal breathing. Great difficulty, however, was experienced in returning the animals to O_2 at one atmosphere pressure after exposure of 3 to 6 hours in O_2 at pressures of 5 atmospheres, even though the decompression was carried out well within the range of safety from bubble formation.

During decompression from prolonged exposure to OHP the respiration not uncommonly diminished, in both depth and frequency, to complete cessation and after a period of apnea, followed by a few short terminal gasps, the animal died. Recompression in O_2 during the apneic period frequently caused a resumption of breathing. This difficulty in returning the animals to atmospheric pressure after prolonged exposure to OHP recalls that encountered in returning animals to normal atmospheres after their prolonged residence in hyperoxygenated air or in pure O_2, at atmospheric pressure. There are, no doubt, some etiological features common to both conditions, e.g., an alteration of pulmonary membranes and perhaps incompletely or slowly reversible changes in the respiratory enzyme

mechanisms of tissue cells; but it may be worthy of note that whereas return to normal air after prolonged exposure to O_2 at atmospheric pressure is attended by hyperpnea and dyspnea, the return to normal pressure after exposure to OHP is at times attended by apnea.

The respiratory response observed during the prolonged exposures to OHP was frequently so very similar to that induced by cold block application to both vagus nerves while breathing O_2 at atmospheric pressure as to suggest that the OHP had effected a functional vagal block, at least in so far as respiration was concerned (Bean and Rottschafer, 1938). These same investigators also found the hyperpnea and the convulsive respiration induced by OHP was not dependent upon either the carotid bodies and sinuses or upon the aortic bodies and mechanoreceptors in the aortic arch, although it was noted that such reflex mechanisms do contribute to the reactions to OHP elicited in the intact animal.

The respiratory response to OHP is not identical in all animals, and, like the susceptibility to the convulsive action of OHP, shows considerable individual variation. In some animals exposed to OHP the breathing after an initial hyperpnea becomes periodic (Bean, 1932). This periodicity varies in degree and type, in some instances very prolonged apneic periods (30 min.) have been recorded. Accompanying this respiratory periodicity are equally pronounced rhythmic changes in volume flow of blood. Occasionally it has been noted that those few animals which failed to respond to OHP by hyperpnea have succumbed early in the exposure; this has been especially true in decerebrate animals, and suggests the importance of the compensatory function of hyperpnea in OHP. It has also been noted (Bean and Rottschafer, 1938) that the respiratory and neuromuscular responses to OHP in animals which were decerebrated under temporary evipal anesthesia were much less pronounced than in those prepared under ether.

Behnke, Shaw, Shilling, Thomson and Messer (1934) and Shaw, Behnke and Messer (1934) have also noted the spasmodic nature of the respiratory response to OHP, as a part of, or very closely associated with, the convulsive seizures in dogs anesthetized with sodium diethyl barbiturate. These authors reported that in dogs which suffered O_2 convulsions, normal breathing was resumed on shifting from OHP to normal air, and that recovery was immediate and complete. In human subjects it was observed (Behnke, Johnson, Poppen and Motley, 1935) that although breathing O_2 at a pressure of 4 atmospheres might cause hyperpnea, severe O_2 convulsions sometimes occurred without any preceding respiratory, circulatory or subjective changes.

3. *Metabolism.* (a) *Respiratory exchange.* Bert (1878) found that both the CO_2 exhaled and the O_2 absorbed by his experimental animals were decreased as a result of exposure to OHP; these changes were accompanied by a decrease in body temperature. The validity of Bert's results has been questioned by Krogh (1916). But Hill and Macleod (1902, 1903a, b, c) also found a diminished CO_2 output and O_2 absorption and a drop in body temperature in mice, rats and young rabbits exposed to O_2 at pressures of one atmosphere and above, and maintained that such metabolic changes are a sign of O_2 poisoning. In further agreement

with Bert these authors observed similar effects were induced by compressed air at pressures above 5 atmospheres.

According to Bert air at a pressure of 10 atmospheres exerts the same effects and gives the same diminution of CO_2 output and O_2 absorption as O_2 at a pressure of 2 atmospheres, but Hill and Macleod (1903c) found air at a pressure of 10 atmospheres to be more damaging than O_2 at 2 atmospheres. They considered that the diminution of CO_2 in the expired air of animals breathing OHP and compressed air at pressures up to 100 pounds ". . . might conceivably be due to one of two causes, to some impediment to the excretion of CO_2 from the blood in the lungs, in which case the CO_2 content of the blood would rise, or to diminished oxidation in the tissues, in which case it would fall. Our present results," they said, "would so far tend to point to the latter as the more probable condition" (Hill and Macleod, 1903a). They later concluded that compressed air at 5 atmospheres and upwards diminished the CO_2 output and increased the loss of body heat. "The lessened CO_2 output is due to the high partial pressure of oxygen which arrests the oxidation processes in the tissues. A partial pressure of 100 per cent atmosphere of oxygen has this effect, and the effect increases with the partial pressure" (Hill and Macleod, 1903b).

In subsequent studies on man concerning exposure to air pressures as high as 75 pounds, Hill and Greenwood (1906) obtained data which ". . . support the conclusion that changes in the percentage of carbon dioxide in the alveolar air depend solely upon physical conditions. No increase or decrease in the pulmonary output of CO_2 occurs. Metabolism then, in so far as it can be determined by an investigation of the alveolar air, is not affected by increasing the barometric pressure. It is scarcely necessary to add that this criterion is by no means adequate to sustain the final conclusion that metabolism is, in fact, unaltered by the atmospheric conditions; so far as it goes, however, it is in favor of such an inference." They concluded, "It is probable . . . the changes in the percentage of carbon dioxide in the alveolar air are conditioned solely by physical variations, and not by an increase or diminution in the respiratory metabolism." Hill (1906, 1912) reiterates conclusions previously stated (Hill and Macleod, 1903b) that compressed air or increased O_2 pressures diminish metabolism. Bean (1929, 1931) found that the O_2 absorption of anesthetized dogs was diminished by their exposure to O_2 at from 3 to 5 atmospheres.

(b) *Nitrogen metabolism; blood chemistry.* Bert claimed that increased O_2 caused a diminution in the urea output. Hill and Macleod (1903c), questioning Bert's urea data on the grounds of insufficient preliminary determinations and because some of the data was frankly suggestive of error, carried out three test experiments on three dogs, one of which succumbed on the second day of exposure to compressed air at a pressure of from +7 to +8 atmospheres. They found no evidence of any consistent alteration in urea output, but it would appear on examination that these experiments, like those of Bert, were not entirely satisfactory and that they offer no very conclusive evidence concerning the effects of OHP on nitrogen metabolism. Shilling et al. (1934) report that dogs exposed to O_2 at about 45 pounds' gauge pressure showed no significant changes in urine

from normal, although in most cases it was of high specific gravity at the end of the experiments.

The changes in blood chemistry reported by some authors may be a reflection of alterations in metabolism induced by OHP. Bert found that the destruction of blood glucose was diminished in animals by their exposure to OHP. Iwanow et al. (1934) reported an increase in blood sugar and dismissed the supposition that O_2 convulsions were of hypoglycemic origin. Somewhat similarly, Shilling et al. (1934) reported that in animals which had had convulsive attacks in OHP, there was an increased glucose and phosphorus content of the blood but that in nonconvulsed animals there was no change. While the elevation in blood sugar and phosphorus found by these authors in the convulsed animals was considered by them to have been the result of the toxic effect of the OHP, they concluded that such elevation was not the cause of either the convulsions or the lung damage found in the animals. Determinations of non-protein nitrogen, chlorides, creatinine, calcium and potassium of the blood showed either no change, or where changes did occur they were apparently not related to convulsive seizures or other symptoms of O_2 poisoning. Ishikawa (1939) reported that the blood sugar was increased, but that the blood lactic acid, albumin, and the colloidal osmotic pressure of the serum was decreased in rabbits which had been exposed to compressed air at from 60 to 130 pounds' pressure. Bean and Haldi (1932) found a reversible increase in blood lactic acid of urethanized dogs exposed to O_2 at pressures of 5 atmospheres and suggested this may have been due to alterations in oxidative mechanisms.

(c) *Body temperature.* In considering changes in body temperature as an index of metabolic alterations induced by exposures to OHP several physical factors are worthy of attention. Hill and Macleod (1903c) reported that the increased thermal conductivity of the compressed gas contributes in large measure to the lowering of the body temperature observed in animals exposed to compressed air or to OHP. In addition to this factor of conductivity, however, there is also the possibility that the environmental temperature changes occurring as a result of rapid compression and decompression introduce significant complications, not only because of the direct effect which such environmental changes would have on body temperature but also because of the influence they would exert secondarily on metabolism and physiological processes, through the changes in body temperature.

The observation (Case and Haldane, 1941b) that the heat developed "due to adiabatic compression" was of such magnitude as to cause discomfort in human subjects is of interest in this connection. Another possible physical source of error and one which may be very significant where body temperature changes are at best not great, is the mechanical effect of pressure on some thermometers. The reviewer has observed that even with pressures as low as 50 pounds this error may amount in some cases to as much as 1°C.

Bert (1878) reported that exposure of animals to OHP caused a drop in body temperature as great as 10°C. but the readings were taken after decompression. Valenzuela (1887) observed that exposure of a pneumonia patient to O_2 at a pres-

sure of about 1.5 atmospheres resulted in a lowering of the temperature to 1.7°C. Thompson (1889) noted a decrease in the body temperature of monkeys, pigeons, guinea pigs and dogs on their return to normal atmospheric pressures after exposure to OHP. A guinea pig which died in convulsions three minutes after removal from the pressure chamber showed a drop in temperature of 14°C. The body temperatures of a dog and a guinea pig which had suffered convulsions on decompression from an exposure to O_2 at a pressure of 4.2 atmospheres for one hour were decreased; both animals succumbed. Thompson, however, stated that the temperature change was "in no wise associated with an increase in the O_2 absorbed." On the other hand the temperature of an alligator which had been exposed to the OHP along with the dog and guinea pig, but which showed no symptoms of O_2 poisoning either during the exposure or on decompression, increased from 51.25°F. to 75°F. (environmental temp. had been 66°F.). Cleveland (1925) reported that frogs were more resistant to OHP than warm-blooded animals. Such results suggest that this greater resistance of poikilotherms to the convulsant and toxic action of OHP is related to inherent metabolic processes as seems to be true also for the greater resistance offered by these animals to the adverse effects of increased O_2 tensions at atmospheric pressure. (See section I.)

No definite change in rectal temperature was observed in dogs during their exposure to O_2 at pressures of from 3 to 5 atmospheres at 25°C. for periods of about 2 hours (Bean, 1931). Ozorio de Almeida (1934a) however found a decrease in rectal temperature of animals exposed to OHP and concluded that a decrease in organic oxidations is the essential characteristic of poisoning by OHP. Dionessow et al. (1934) also found a decreased temperature in exposures to OHP. Hederer and Andre (1940) noted a small decrease about 1°C in the body temperature of rabbits on their return to normal atmospheric conditions after exposure to OHP.

(d). *Alterations in metabolism induced by artificial means and their effect on the response to OHP.* Some further data concerning the relationship between metabolism and the effects of OHP have been obtained from various experiments in which exposure to OHP was combined with procedures which are known to, or thought to, alter metabolism. Ozorio de Almeida (1934b), in attempting to increase the destructive action of OHP on tumors through metabolic changes, used, in preliminary experiments, injections of dinitrophenol, benzole, paradichlorobenzene, quinine, nitrate and nitrite of sodium, methylene blue, prolan, and also a preparatory period of anoxemia. Starvation was found to increase the resistance of the animals to poisoning by O_2 at high pressure. This effect of the nutritive state of the animal on its susceptibility to O_2 poisoning has been confirmed by Campbell (1937a, b) and Hederer and Andre (1940).

In further attempts to alter the susceptibility of animals (80 gram rats) to O_2 poisoning, Campbell (1937b, 1939) administered a number of preparations; thyroxin (0.4 mgm.), dinitrophenol (1.5 mgm.), actetrahydro-B-naphthylamine (0.5 cc., 1 per cent), adrenaline (0.02 mgm.), pituitary extract (posterior lobe, above 3.5 units), insulin (0.025 U), and eserine (0.045 mgm. administered with atropine 0.075 mgm.), and ergotomine (slight effect), enhanced the O_2 poisoning.

Glucose injections did not alter the effects of OHP, which is perhaps significant in view of the observation that a well-fed animal is more susceptible to O_2 poisoning than one which has been starved. Histamine, curarine chloride, acetylcholine (with eserine and atropine) were also without effect on O_2 poisoning, although some increase in histamine has been found in the blood in animals poisoned by O_2. Urethane in the usual doses was found to have no effect on O_2 poisoning, but dial did exert some slight protective action.

Barbiturates have also been reported (Hederer and Andre, 1940) to exert a protective action, and Behnke, Shaw, Shilling, Thomson and Messer (1934) believed the convulsive attacks were modified by barbital anesthesia—only two out of nine dogs so anesthetized had convulsive seizures. In experiments where Evipal was tried as a transient anesthesia for decerebration (Bean and Rottschafer, 1938) the animals were less reactive to subsequent O_2 exposures than were those decerebrated under ether or urethane; Evipal, it appeared, exerted some residual effect, but whether this lack of response represents a protective influence may perhaps be debated, since some animals that fail to show an increased respiratory reaction succumb early in the exposure to OHP. The protective effect of anesthetics is thought by Campbell (1939) to be due to their lowering the metabolism of the organisms. Strychnine has been found to accentuate the O_2 convulsions (Hederer and Andre, 1940).

Campbell (1937a, b) interprets the fall in body temperature which has been reported by many investigators to accompany O_2 poisoning as a protective reaction on the part of the animal to the increased O_2 tension. He found that when the environmental temperature was raised to 38°C. few rats survived thirty minutes' exposure to O_2 at pressures of six atmospheres, whereas in an environmental temperature of 24°C. there were few deaths. Removal of the thyroid gland was found to increase the resistance of the rats to O_2 poisoning, even when the environmental temperature was raised to 33°C. Hypophysectomy had some but less protective action than thyroidectomy. Comparable enhancement of the toxic action of OHP by elevation of the environmental temperature was also found by Williams and Beecher (1944) in experiments on Drosophila at 34.2°C., the rate of poisoning by O_2 at a pressure of 5 atmospheres was about 8 times as rapid as at a temperature of 14.4°C.

4. *Circulation. Blood pressure, pulse rate.* The circulatory effects of breathing OHP will depend, in large measure, upon the general response of the animal to OHP; e.g., it would be expected that the blood pressure response in an animal which had reached the convulsive stages of O_2 poisoning with its violent motor responses might be quite different from that in an animal which had not attained that degree of intoxication. It may be well, therefore, to keep in mind the possibility that the circulatory changes which occur as a result of violent motor responses precipitated by OHP may completely mask some of those circulatory changes which are truly representative of the more immediate action of OHP.

Hill and Macleod (1903c) found that the blood pressure and pulse rate of an anesthetized dog were unchanged by rapid compression to, or decompression from, an O_2 pressure of 3 atmospheres. Similarly the circulation in a chloralized

rabbit was not altered by exposure to O_2 at a pressure of 6 atmospheres, but rapid decompression was attended by a rise in blood pressure which, the authors suggested, was due to the noise of the escaping air. This absence of any distinct change in blood pressure during compression to O_2 pressures as high as 6 atmospheres has been confirmed in anesthetized and decerebrate dogs (Bean, 1929, 1931; Bean and Rottschafer, 1938). In 60 experiments (urethane anesthesia) in which the duration of the exposure to OHP was such as to avoid pronounced convulsive seizures (about one hour), the blood pressure increased in five instances while in the others there was either no significant change or a slight decrease. These results would seem to indicate that, except for a slight tendency to rise, the blood pressure is not appreciably affected by O_2 at pressures of from 3 to 6 atmospheres if the animal has not approached the convulsive stage.

In a study of the circulatory effects of compressed air on 13 human subjects (experienced divers) Hawkins, Shilling and Hansen (1932) found that exposure to compressed air (an O_2 equivalent of about 1.2 atmospheres) caused the average pulse rate to rise from 68 per minute to 73 per minute; the average systolic and diastolic blood pressures increased slightly (2 mm.), but the pulse pressure and circulation were not appreciably changed. Case and Haldane (1941b) reported that exposure of human subjects to compressed air (O_2 equivalent of 2 atmospheres) caused an increase in heart rate, but that the changes in the systolic blood pressure were not uniform—some showed an increase while others showed a decrease.

Shaw, Behnke and Messer (1934) observed that in dogs anesthetized with sodium diethylbarbiturate, O_2 at 4 atmospheres caused an immediate or delayed drop in blood pressure which persisted for as long as 3 hours, but usually this fall was rapid and terminated in the death of the animal in less than an hour from its onset. These authors maintained that ". . . in every case in which convulsions occurred there was a preceding fall in blood pressure and conversely we may expect that a fall in blood pressure will be followed by convulsions." They concluded that a drop in blood pressure was the first sign of the toxic action of OHP. However, where artificial hyperventilation was performed during the exposure to OHP in an attempt to keep the alveolar CO_2 low, the blood pressure was maintained at about normal level except for an initial drop in blood pressure attributed to "the mechanical interference with the filling of the right heart when the dog resisted the rhythmic action of the respirator."

In later work (Behnke, Johnson, Poppen and Motley, 1935) it was reported that there occurred no changes in blood pressure of four men as a result of their exposure to O_2 at pressures as high as 4 atmospheres, except in two subjects. In one of these there was a drop in blood pressure; in the other there was no change in blood pressure or pulse rate for 44 minutes of exposure, at the end of which time there developed without any warning, violent convulsions from which consciousness was regained twenty minutes later. The blood pressure was apparently not followed during this seizure but it can hardly be assumed that it remained unchanged. The absence of any premonitory drop in blood pressure in this second subject emphasizes the inadequacy of the generalization that the convulsive seizure is heralded by a drop in blood pressure.

Data from a subsequent series of experiments (Behnke, Forbes and Motley, 1936) show that in the first hour of breathing O_2 at 3 atmospheres—the systolic pressure in human subjects had fallen from 132 to 100 mm. Hg while the diastolic pressure of 86 mm. Hg had changed but little. However, after an exposure of three hours the pressure had gradually risen to 150/104. The authors state that "impending collapse was always signalized by an increase in pulse rate, rise of both systolic and diastolic pressure of 15 to 20 points. . . ." This latter observation is in line with other experimental findings (Bean, 1931; Bean and Rottschafer, 1938) derived from urethanized and from decerebrate dogs in which a gradual rise in blood pressure preceded, and a further rapid rise in blood pressure accompanied, the onset of convulsive seizures; similar blood pressure changes occurred after the denervation of carotid sinuses and bodies. It has been pointed out (Bean and Rottschafer, 1938) that blood pressure changes—particularly a drop—are not a reliable index of the onset of O_2 poisoning; the toxic effects of OHP are continuous and gradual in their development and one of their earliest manifestations is an alteration in breathing.

Numerous workers have reported that exposure to OHP causes a slowing of the pulse rate (Bert, 1878; Hill and Macleod, 1903c; Hill, 1912; Dautrebande and Haldane, 1921; Bean, 1929, 1931; Behnke, Johnson, Poppen and Motley, 1935; Whitehorn and Bean, 1942). This seems to justify the generalization that OHP causes a slowing of the heart but one qualification for the acceptance of this generalization would appear again to be an absence of the complicating features of convulsive seizures or collapse. A reversible slowing of the pulse was found (Bean, 1931) in urethanized dogs exposed to O_2 at pressures of from 3 to 5 atmospheres for periods of 45 to 90 minutes, provided no convulsions occurred. Behnke, Johnson, Poppen and Motley (1935) report that no significant alterations in pulse rate occurred in a man exposed to 4 atmospheres of O_2 for 43 minutes. In another of their subjects there was an absence of radial pulse during collapse after a similar exposure, and although Behnke, Forbes and Motley (1936) found that in a 3 hour exposure to O_2 at 3 atmospheres pulse rate fell from 90 to 57 per minute, it subsequently rose and led those authors to conclude that an increase in pulse rate always signalizes "impending collapse." An increase in pulse rate just preceding and even during convulsive seizures has been recorded in decerebrate dogs (Bean and Rottschafer, 1938).

It has been noted (Bean and Rottschafer, 1938) that the tachycardia which results from vagal sectioning is not prominently altered by the subsequent exposure of the animal to OHP. This was interpreted as an indication that the bradycardia which occurs so commonly in animals with intact vagi during exposure to OHP for periods of subconvulsive duration is mediated via the vagi, and that any slowing influence which might possibly be exerted by the OHP directly on the heart or through the sympathetic innervation may be completely masked by vagal sectioning.

The increase in heart rate which has been observed so frequently with the onset of O_2 convulsions in animals with intact vagi and which follows the initial cardiac slowing induced by the OHP may perhaps be explained as due to a secondary chemical blockage of vagal fibres (Bean and Rottschafer, 1938). This in-

terpretation of the late tachycardia in exposure to OHP finds support in the report of Hill and Macleod (1903c) that in the frog heart the vagus nerve endings seemed to be paralyzed by OHP.

Bert (1878) noted that the hearts of animals which had succumbed to O_2 poisoning were still reactive to artificial stimuli but he recognized that OHP affected cardiac function; in his protocols on the frogs which had been exposed to OHP, he made the notation that the ventricular pulsations were irregular and few in number, whereas the auricles continued to beat (40 per min.). Such an alteration in cardiac rhythm might, of course, have occurred as a terminal change—particularly since the frog heart is so susceptible to changes in pH (Clark, 1913; Daly and Clark, 1921), but it suggests that the OHP may have caused heart block, although no point was made of this. Bert also demonstrated that isolated frog's heart suspended in the vitreous humor of a dog was not only completely arrested by exposure to O_2 at pressures of 10 atmospheres for 6 hours but that it lost its excitability, while the control hearts, especially the auricles, remained active and excitable. He concluded that the pace setter or ganglion of the heart was arrested much more rapidly than occurred in normal air and that the muscular elements and nerve ganglia were killed by OHP.

Hill and Macleod (1903c), however, found that the heart of a frog exposed to O_2 at pressures as high as 50 atmospheres was not rapidly poisoned and continued to beat more than an hour under such pressure. Inhibition of such hearts by artificial excitation of the sino-auricular junction was readily induced, but excitation of the vagus was without effect. Lehmann (1884) found that excised frog hearts did not stop beating until after 9 hours of exposure to O_2 at pressures of from 10 to 14 atmospheres. Bean and Bohr (1938a,b) and Bohr and Bean (1939) found that O_2 at from 70 to 80 pounds' gauge pressure acting on excised frog ventricles caused an initial increase followed by a late decrease, in the contraction strength, a delayed slowing in frequency, and an eventual cessation of automatic contractions. The pace setter was observed to be much more susceptible to the OHP than the contractile mechanism; the muscle remained excitable to artificial stimuli long after cessation of the normal beat. The conductivity appeared to be initially improved; possible late effects were not apparent in these experiments. In mammalian hearts it has been shown from E.K.G. records (Bean and Whitehorn, 1941; Whitehorn and Bean, 1942) that O_2 at pressures of about 5 atmospheres does not cause any very rapid alterations in the conductive mechanisms but the P–R interval is frequently very distinctly prolonged and some features simulating those observed during low O_2 administration are present in the longer exposures.

Blood vessel caliber and volume flow of blood. If, as the evidence presented in section I would indicate, O_2 at atmospheric pressure induces a slight vasoconstriction, it would be only reasonable to suppose that a similar but more pronounced effect might be induced by OHP. The problem, however, is not quite so simple, since OHP introduces other complicating influences.

The experiments of Poiseuille (1835) and of Hill and Macleod (1902) indicate that OHP administered by the use of highly compressed air causes no alteration

in caliber of peripheral vessels. Bert (1878), in examining the eye ground of dogs convulsed by OHP, noted they were strongly injected, which observation suggests vasodilatation rather than constriction. Dautrebande and Haldane (1921), using an alteration in alveolar CO_2 as a criterion of a changed blood vessel caliber, have maintained that the breathing of OHP induces a central vasoconstriction which acts to protect the C.N.S. against the toxic effects of excess O_2. The validity of their argument may be seriously questioned, however, especially since in their experiments no attempt was made to control either pulmonary ventilation or metabolism. (See section I.)

A more direct method of determining the influence of OHP on the volume flow of blood through the brain, based on the experimental evidence that the flow through the carotid artery parallels the vertebral flow (Bronk and Gesell, 1927) was used in more recent investigations (Bean, 1929, 1931). In 28 experiments on urethanized dogs the volume flow changes in the carotid artery were followed continuously throughout exposures to O_2 at pressures of about 5 atmospheres for periods of from 30 to 90 minutes; no significant alterations were found except in three animals in which there was a small increase in volume flow. Such results would seemingly justify the conclusion that those vessels which distribute the carotid blood are not significantly constricted by breathing O_2 at 5 atmospheres for the periods mentioned, and that if there is any sharply localized portion of the brain which suffers vasoconstriction, the resulting changes in blood flow to that area must be so small as to be masked by dilatation elsewhere.

Further evidence that breathing OHP does not cause central vasoconstriction is found in the observations of Behnke, Forbes and Motley (1936) that the caliber of the pial arteries of a cat was not appreciably changed by the animal's exposure to O_2 at a pressure of 4 atmospheres.

There are experimental data which indicate that OHP may cause central vasodilatation, rather than constriction, because of the complicating involvement of CO_2. It has long been recognized that CO_2 acting directly on blood vessels may cause a local vasodilatation. Moreover, there is now very convincing evidence that breathing gas mixtures containing increased CO_2 at atmospheric pressure results in a very pronounced dilatation in the pial vessels of cats, and that such dilatation overshadows any slight constrictive action which increased tensions of O_2 at atmospheric pressure might exert (Wolff and Lennox, 1930). Similar dilating action of CO_2 on cerebral vessels was found by Forbes (1928). The results of experiments by Gibbs, Gibbs and Lennox (1935) show that cerebral blood flow (internal jugular vein) in man is increased by breathing gas mixtures high in CO_2 content and that any vasoconstricting influence of O_2 is masked by the greater dilating effect of CO_2. Schmidt (1934) and Schmidt and Pierson (1934) reported that CO_2 causes vasodilatation in hypothalamic and medullary tissues of the brain.

The importance of CO_2 as a causal or contributing factor in poisoning by OHP has been recognized by numerous investigators (Thompson, 1889; Gesell, 1923; Bean, 1929, 1931; Campbell, 1929; Hill, 1933; Shaw, Behnke and Messer, 1934) and the experimental data now available leave little doubt but that under OHP there

is an accumulation of CO_2 in the tissues; this CO_2, in conjunction with other and possibly more direct effects of OHP might well result in a central vasodilatation.

Behnke, Forbes and Motley (1936) found that CO_2 administered to a cat during its exposure to O_2 at a pressure of 4 atmospheres caused an immediate and striking dilatation of the pial vessels. Inspection of their plotted data (fig. 2 below) from one experiment reveals two additional features not mentioned by the authors but which may be of considerable importance. First: the vessel diameter when the animal was exposed to air at 4 atmospheres' pressure was greater than when exposed to air at normal pressure, which suggests that compressed air or its increased O_2 tension caused vasodilatation. Second: during the first five minutes of breathing OHP the gradient of calibre decrease was temporarily sharper than that obtaining under an equal pressure of air, but following this, the vessel calibre remained constant at its precompression value until CO_2 was administered some few minutes later. The sequence of changes in this second feature might be interpreted as indicative (1), that OHP causes an initial vaso-

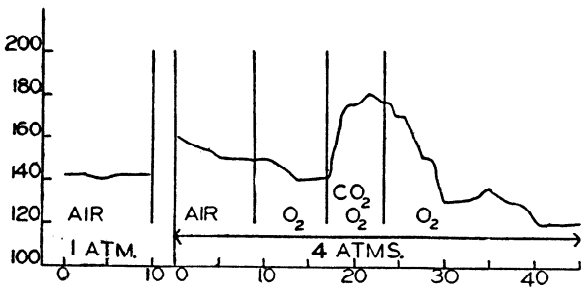

Fig. 2. Changes in the diameter of a pial arteriole of a cat breathing a 2 per cent carbon dioxide (equivalent to 8 per cent carbon dioxide at 1 atmosphere) and 98 per cent oxygen mixture at 4 atmospheres' pressure. Ordinate, diameter in microns; abscissa, time in minutes. (Behnke, Forbes and Motley. Am. J. Physiol. **114:** 436, 1935.)

constriction but that this is shortly thereafter nullified by some counteracting influence which gradually comes into play; (2), that the counteracting influence may be an accumulation of endogenous CO_2 in the tissues.

In view of these CO_2 effects, the progressive drop of blood pressure which has been observed to precede the onset of O_2 convulsions in dogs anesthetized by Dial (Shaw, Behnke and Messer, 1934) might suggest a generalized vasodilating action of accumulating CO_2. On the other hand, the maintained or gradually elevated blood pressure of urethanized dogs in the earlier stages of exposure to OHP (Bean, 1931) and the sharp rise during the convulsive seizures (Bean and Rottschafer, 1937) would suggest that the vasodilatation which might arise from the CO_2 accumulation during OHP exposure is not one of a profound generalized nature and that with the onset of strong C.N.S. effects, any peripheral vasodilatation is counteracted by vasoconstriction via the centers.

Evidence of a late peripheral vasoconstriction is found in the blanching of the skin in men about to suffer collapse from OHP (Behnke, Johnson, Poppen and Motley, 1935). A similar blanching of the ears of rats just before, during and

after convulsive seizures in OHP has been commonly observed by the reviewer. If such a peripheral vasoconstriction occurs over any very extensive area it might, of course, function to maintain or even to increase rather than decrease the blood flow to the higher centers. But in any case an evaluation of the evidence as a whole does not justify the conclusion that exposure to OHP causes predominant central vasoconstriction and decreased flow of blood to the C.N.S.

Regardless of the state of constriction or dilatation of the blood vessels in the C.N.S. the venous blood in animals exposed to OHP comes from the brain in a highly oxygenated state, as is seen from its bright red color and from the fact that such blood placed under atmospheric pressure froths as a result of the escape of the excessive O_2 in solution in the plasma (Bean, 1929, 1931). Such observations clearly indicate that the organism fails to protect its C.N.S. tissues from OHP by vasoconstriction and that under such conditions the oxyhemoglobin is not normally reduced. Instead of arguing that a vasoconstrictor effect of OHP performs a protective function for the C.N.S. one might even more logically argue that greater protection might be derived from a vasodilatation which would facilitate the removal of the accumulation of CO_2 and metabolites.

5. *Ferments, Micro-organisms and Enzymes.* Bert reported that the potency of salivary diastase was not altered by its exposure to hyperoxygenated air at a pressure of about 15 atmospheres for 5 days. Similarly pepsin, invert ferment of yeast, myrosin and emulsin remained unaltered. In fact according to Bert, none of the soluble ferments, referred to by him as "false" or "non-formed" ferments because they ordinarily retained their activity after extraction from their living source, were adversely affected by their exposure to OHP. The toxicity of scorpion venom was likewise reported to be unaltered by such treatment. Bert argued that this absence of any effect of OHP on these substances was to be expected because they were not living cellular structures. The "true" ferments, which in Bert's terminology were living cellular organisms, were however killed by OHP.

In his study on micro-organisms Bert reported that those responsible for the souring of wine were killed by hyperoxygenated air at a pressure of 10 atmospheres; putrefactive processes were likewise said to have been prevented due to the destruction or inhibition of the organisms involved. Blood was preserved for days by hyperoxygenated air at a pressure of about 14 atmospheres but hemolysis was not prevented. The coagulation of milk, too, was claimed to have been arrested by compressed air. Eggs, meat and bread were likewise preserved, although they turned acid in reaction, probably due, it was suggested, to lactic acid. Molds and yeasts were said also to be killed by hyperoxygenated air at increased pressure.

Bert reported that what he called "viruses" remained unaffected by their exposure to superoxygenated air at increased pressure. This he maintained demonstrated unequivocally that they were not living things and that their potency was not dependent upon the presence of living organisms or cells. Unfortunately the "viruses" he studied were derived from three diseases ("vaccine"—probably vaccinia; glanders, and anthrax), two of which, anthrax and glanders, are not of

virus origin, as he had erroneously assumed. Although Bacillus anthracis was discovered two years before LaPression Barometrique was published, the glanders bacillus was not demonstrated until 1882. Bert's own experimental finding that glanders bacillus remained virile after 6 days' exposure to hyperoxygenated air at a pressure of 20 atmospheres constitutes evidence against his own strong contention that such O_2 pressures kill every living thing. Spoilage of fruit ("Blettissement des Fruits") was reported to have been accelerated, rather than stopped, by exposure to hyperoxygenated air at high pressure; Bert concluded therefore that that condition could not be caused by any cellular form of life and suggested that it was due to some direct oxidation.

Following this early work of Bert, various reports appeared concerning the adequacy of OHP as a sterilizing agent. Schaffer and v. Freudenreich (1891), following up some work of d'Arsenval (1891) on the effects of CO_2, failed to confirm Bert's contention that OHP killed organisms in milk. DeLavallee (1898), however, found that both aerobic and anaerobic bacteria could be killed if the cooled milk were exposed to CO_2 at from 5 to 6 atmospheres' pressure for from 4 to 5 hours and then, after the CO_2 had been permitted to escape, re-exposed to O_2 at 5 atmospheres for 5 hours. Milk so treated, it was claimed, could be kept in a fresh condition during transportation by maintaining an O_2 pressure of 2 atmospheres in the container. The practicability of the old idea of milk preservation by OHP seems to be indicated by the issuance of a U.S. Patent to K. Richter in 1941 for a method involving OHP.

Berghaus (1907) found that while 5 of the 20 different micro-organisms he studied were killed by O_2 at pressures as low as 2 atmospheres, 15 remained viable after a 24 hour exposure to 35 atmospheres. He also reported that CO_2 at high pressures was a much more effective lethal agent than was OHP. Cleveland (1925) demonstrated that many protozoa were readily killed by O_2 pressures at 3.5 atmospheres. He also found there was a differential susceptibility between some protozoa and their hosts and suggested that this observation might be put to practical use in the defaunation of the hosts. Such procedure has been carried out with some degree of success on silkworms by Gibbs and Chen (1929). Thaysen (1934) reported that the growth of 4 micro-organisms which he investigated was retarded by O_2 at pressures of 10 atmospheres, and that if the temperature were increased slightly above that for optimum growth, O_2 at 10 atmospheres' pressure became lethal for these organisms. Thaysen's observation on micro-organisms is in accord then with those made on animals by Faulkner and Moore (1927) and Campbell (1937a, b) on the increased potency of O_2 toxicity at increased temperature. The growth of Pneumococcus type I was found to be completely inhibited by exposure for 24 hours to O_2 at pressures as low as 900 mm. Hg and none of these organisms survived exposures to O_2 of 3650 mm. Hg (Bean, 1941).

These reports of experiments on micro-organisms are of interest for several reasons. They clearly indicate that the toxic action of O_2 at high pressure is not limited to organisms of higher order or to animals having R.B.C.'s and a circulatory system and they provide experimental basis for seriously questioning

Bert's conclusion that no living thing can endure an O_2 tension equivalent to that of 20 atmospheres of air. That this contention of Bert's is at least in need of some qualification is indicated not only by his own experiment on glanders but also by the fact that the cells of swim bladders in deep sea fish are apparently immune to the injurious action of O_2 even at extremely high pressures. The swim bladders of deep sea fish contain O_2 in concentrations as high as 84.6 per cent (Schloesing and Richards, 1896). At depths of 4500 feet where these creatures live the pressure is in the neighborhood of 136 atmospheres which in terms of partial pressure of O_2 would be about equivalent to 115 atmospheres of pure O_2.

The experiments on micro-organisms also show that in these lower forms of life as well as in higher there is a wide individual variation in susceptibility to O_2 poisoning. While such variation may be due in part to structural characteristics, it suggests that differences in the respiratory enzyme systems may be responsible. The reports that CO_2 and OHP in combination are more destructive to micro-organisms than OHP alone are in accord with the observation that small amounts of CO_2 are particularly damaging to warm-blooded animals and points to the importance of increased CO_2 on primary cellular processes under such conditions.

6. *Isolated Tissue. Iris.* Pupillary dilatation has been a common finding in animals exposed to OHP (Bert, 1878; Bean, 1931; Bean and Rottschafer, 1938). Kodama (1937) found similar effects in air at high pressure; Behnke, Forbes and Motley (1936) reported that in addition to causing a contraction of visual fields, OHP induced pupillary dilatation. This change might, conceivably, be interpreted as arising from some effect of OHP on the autonomic nervous system, from a release of humoral substances into the circulation, or from a local action on the effector itself. In order to investigate these possibilities, sphincter and radial muscles of beef iris were exposed to O_2 at pressures of from 5 to 6 atmospheres (Bean and Bohr, unpublished data); such exposures caused a reversible decrease in tonus. It was concluded therefore that the central nervous or hematogenous connections are not essential to the occurrence of the pupillary dilatation induced in animals on their exposure to OHP, although in all probability nervous and hematogenous, as well as local effects of OHP, contribute to the induction of that response.

Intestinal muscle. Further experimental evidence bearing on the question of the site of action of OHP on smooth muscle is found in studies on isolated rabbit intestine (Bean and Bohr, 1940); the exposure of longitudinal duodenal muscle to O_2 at about 75 pounds' gauge pressure resulted in a progressive loss in tonus, a decrease and irregularity in the amplitude of the spontaneous rhythmic contractions, and a decreased frequency of this rhythm to a point of periodic cessation interspersed by spasmodic unsustained increase in tonus. Pyloric sphincter tonus was also diminished by OHP. These tonus changes in both longitudinal and sphincter muscles were reversed by decompression.

Atropinization of isolated duodenal and pyloric sphincter muscle preceding compression failed to alter the response to OHP. It was inferred, therefore, that the peripheral influence of OHP on smooth muscle is due neither to a stimulation of intrinsic nerve fibers nor to an involvement of acetylcholine but rather

to some more direct action on the effector cells themselves; the possibility, however, that effects may be mediated by other means in the intact animal was not dismissed. Tests of the bath solution showed no increase in lactic acid.

The response of longitudinal duodenal muscle to OHP was found to be so very similar to that induced by low O_2 tensions and by cyanide as to suggest that it is caused by conditions approximating those of anaerobiosis arising from a poisoning of respiratory enzymes. But the finding (Bean and Bohr, unpublished data) that OHP caused a sharp drop in the tonus of the pyloric sphincter (rabbit) whereas cyanide induced little or no change in that tissue, indicates that the mode of action of OHP is not identical with that of cyanide and that it must involve some other mechanism than the cyanide sensitive cytochrome-oxidase enzyme system. A comparison of the effects of OHP on longitudinal duodenal muscle and on pyloric sphincter showed that while the tonus of both tissues was decreased by OHP, the tonus of the sphincter was much more markedly and rapidly depressed than was that of the longitudinal duodenal muscle. Incidentally, this difference in the reaction to OHP, together with the inverse effects induced in these same tissues by cyanide, is highly suggestive that the maintenance of tonus in these two tissues is dependent upon different enzyme systems.

Striated muscle and nerve. Since sectioning of the motor nerves relaxed the spastic muscular contractions of O_2 convulsions, Bert concluded that the seizures were not caused by the action of the O_2 on the muscles themselves. He also observed that striated muscle in frogs which had succumbed to O_2 at pressures of 3 atmospheres were responsive to direct artificial stimulation, although spinal reflexes could no longer be elicited. In frog muscle-nerve preparations suspended for 26 hours in hyperoxygenated air at a pressure of 15 atmospheres, it was found that the excitability of the nerve (as determined by muscle reaction) was lost; yet the muscle itself was still reactive to direct stimulation. These results suggest that striated muscle is relatively more resistant to the adverse action of increased O_2 pressure than is the C.N.S. or nerve fiber, but they do not rule out the myoneural junction as the possible vulnerable point of attack on the nerve-muscle preparation.

Valuable as Bert's experiments on isolated tissues are, they are very few in number because, as he said, the results of the few agreed so well with his previous expectations that a larger number was deemed unnecessary. His results may not truly represent the effects of OHP alone since his tests were made after rapid decompression of the preparations to normal atmospheric pressure following their exposure to very high pressures. Furthermore, in these, as in so many of Bert's experiments on O_2 poisoning, highly compressed air or compressed hyperoxygenated air was used rather than pure O_2, on the assumption that the effects of compressed air are due only to the partial pressure of the contained O_2.

Hill and Macleod (1903c) performed several experiments on isolated striated muscle and nerve preparations in which the tissues were exposed to O_2 at pressures as high as 50 atmospheres; no change from the normal was found in the contraction curve of the gastrocnemius muscle recorded under pressure, but the curve of the sartorius showed some slight alteration. These data although

limited, again suggest that striated muscle and nerve are quite resistant to the deleterious action of OHP.

The scanty data concerning the effects of OHP on isolated muscle and the methods by which they were obtained called for a more careful and extensive series of experiments. Bean and Bohr (1938) using photographic methods carried out experiments on isolated striated muscle, muscle-nerve and reflex preparations of frogs. It was found that exposure to O_2 at pressures of about 5 atmospheres caused an initial increase in the height of contractions elicited by stimulating the muscle directly or through its nerve; subsequently, however, there occurred a slowly progressive decrease in height. These effects were found to be only partially reversible. The nerve fiber and the myoneural junction were apparently no more profoundly affected by the high O_2 than was the muscle itself. This toxic action of OHP was attributed to a poisoning of respiratory enzymes. Isolated cardiac muscle has also been shown to be somewhat similarly affected by OHP (Bohr and Bean, 1939).

7. *Pathology.* Although Bert was aware of the view that breathing O_2 in high concentrations at atmospheric pressure caused lung damage, he made no extensive search for possible lung damage in his experimental animals which had been exposed to compressed hyperoxygenated air or to OHP. In the rare examinations he did make he found neither congestion nor ecchymoses either in the lungs or in the nerve centers, but the eyes of a dog which had suffered convulsions on rapid decompression revealed hemorrages.

In sparrows he found pathologic changes in the diploe and meninges which he likened to those seen in asphyxia. He says, "On ne trouve ni congestions, ni ecchymoses, dans les poumons et dans les centres nerveux. Seulement, d'une manière constante, chez les moineaux, on voit le diploé crânien rempli d'un épanchement en piqueté, en taches plus ou moins grandes, ou même en nappe, envahissant toute la région occipitale, et, dans les cas les plus violents, toute l'etendue du crâne. Ces suffusions sanguines, dont le mécanisme ne me parait point facile à expliquer, sont constantes dans l'empoisonnement par l'oxygene. Elles arrivent bien avant le moment de la mort. Mais elles ne sont pas spéciales à ce genre de mort, et dans les expériences qui précèdent on les trouve signalées, même dans l'asphyxie simple, sous diminution de pression."

Bert's experimental procedures in his study of high O_2 pressure effects were, with few exceptions, such that any pathology which he might have found could not be safely interpreted as having been caused by the O_2 alone. The decompression rates in his dog experiments were entirely too fast (many of them were abrupt "brusquement") to ensure the absence of embolism even if almost pure O_2 had been the compression medium, to say nothing of his experiments in which the O_2 content was only about 60 per cent. Furthermore in most of these experiments the CO_2 was permitted to accumulate in the respired gas; in one experiment the CO_2 content of the respired gas reached 12.9 per cent. Both of these complicating factors may have contributed to the pathology he described.

The first report that OHP caused lung pathology is apparently that of Thompson (1889). A guinea pig and a dog which had had convulsions under O_2 pres-

sure and had died a few minutes after decompression, showed at autopsy, "great pulmonary congestion" and "over distention of the right heart." The other viscera were "exsanguinated." The decompressions were carried out gradually thus eliminating possible complications from bubble formation.

Smith (1897a, b) found that a mouse breathing O_2 at pressures of about 2 atmospheres died within 24 hours; its lungs at autopsy were congested, consolidated and sank in water; the alveoli were almost completely filled with exudate, and the blood vessels were extremely congested. These pathological changes Smith thought, occurred early in the exposure. The higher the pressure the shorter was the time during which the lungs were able to withstand the effects of oxygen. Smith claimed that exposure of animals to O_2 at from 170 to 180 per cent of an atmosphere altered the lungs so that they could not "actively" absorb O_2.

In his later work Smith (1899) demonstrated that even at very moderately increased pressures of O_2 the lungs become "inflamed"—effects which are reminiscent of the early reports of Lavoisier and Priestley. In O_2 at 128.9 per cent of an atmosphere mice became sluggish after 40 hours and died in 69 hours; the lungs at autopsy showed consolidation and congestion. There was also congestion in the liver, spleen and kidneys. The more characteristic pathology which Smith found from exposures to O_2 at pressures of between one and two atmospheres as well as for higher pressures was as follows: "The lungs were deeply congested, and sank in the fixing fluid . . . . Spleen slightly enlarged. Other organs normal. On microscopic examination, the tissues of the lungs showed intense congestion in the large and small blood vessels. The alveoli were to a great extent filled with an exudate, which was granular and fibrillated in appearance, but did not give the fibrin stain by Weigert's method, nor with eosin. The Weigert's stain showed one or two streptococci. These, however, were exceedingly few in number, and as the mice died overnight in a somewhat warm atmosphere, their presence was probably accidental. There were no leucocytes in the exudate. The pneumonic condition was universal, and could therefore be compared only with the earliest stages of croupous pneumonia. The exudate itself was probably the cause of the embarrassed respiration and the animal's death. It is inconceivable that with inflammation so extensive, the animal could have survived until the process had developed farther." Mice exposed to O_2 pressures at from 3 to 3.5 atmospheres became dyspneic and when taken from the chamber after about 10 hours died immediately without convulsions; the lungs showed these same characteristic changes.

Smith's experiments led him to conclude that the action of OHP could be divided into two phases: "The one consisting in the slowly developing inflammatory effect seen most prominently in the lung tissue. The other a rapidly developing effect on the nervous tissue, which we may in the meantime describe as functional. . . . Both effects persist after the animals have been restored to ordinary air, and this, since it is frequently inconsistent with recovery, we may regard as indicating a profound change in the tissue cells." Smith emphasized that the transition to the pathological stage in the lung was imperceptible. His claim that this lung damage temporarily protects the C.N.S. from the effects of

breathing OHP, not substantiated by some more recent investigators, has been misinterpreted by some O_2 therapeutists as an argument that a *lung* suffering from penumonia is less susceptible to the damaging effects of increased O_2 tensions than is the normal lung.

Hill and Macleod (1903c) confirmed the findings of Thompson and of Smith. They described changes which in the early stages were characterized chiefly by congestion of the alveolar capillaries but later hemorrhagic exudation and consolidation were present. These authors say, "To the naked eye the lungs present in the early stages a suffused redness. Patches of more intense exudation occur in the apices and edges of the lungs. At a later stage the congestion passes into typical hepatization, the lungs sink in water and are of a dark purple colour. The penumonia is patchy if quickly, and universal if slowly developed." In prolonged exposure to O_2 at pressures of from 3 to 5 atmospheres, lung changes such as described by Hill and Macleod were observed in anesthetized dogs (morphine and urethane) by the reviewer in 1929 and these together with the occurrence of convulsive seizures necessitated the use of relatively short exposures for the investigation of the problem then in hand. Phillips (1931) also found that exposure of animals to OHP caused penumonia.

Shilling and Adams (1933) observed lung changes in animals which had been exposed to OHP, which they described as hyperemia, severe congestion and edema, hemorrhagic exudation, transudation, and acute hemorrhage into the alveoli and tissue spaces. Some lungs were almost solid from hemorrhage and sank in water. The microscopic studies of the brain and nervous tissue were negative. The authors were convinced that lung damage was not the cause of the convulsive seizures because there was "practically no gross lung damage in animals autopsied immediately after the first convulsion occurring early during exposure to high pressures of oxygen. In several instances animals went on to death under high-pressure oxygen with lungs that were not sufficiently damaged to account for convulsions due to asphyxia."

These experiments of Shilling and Adams, directed toward a study of the use of OHP in the decompression of divers, led those authors to the opinion that men exposed to increased tensions of O_2 would, in all likelihood, have early subjective warning of impending lung damage and convulsive seizures because of the probable irritation of nasal and pharyngeal tissue together with general restlessness. It was thought that "Even after a severe convulsion, recovery would probably be rapid and complete if the exposure were immediately terminated." Behnke, Shaw, Shilling, Thompson and Messer (1934) observed pulmonary congestion and varying degrees of atelectasis, but "hemorrhage or edematous exudation into the alveoli or bronchi did not occur," in anesthetized (barbiturate) dogs exposed to OHP.

The findings of Hederer and Andre (1940) are in essential agreement with those described by earlier investigators and these authors maintain that the pathology induced by OHP is the same as that induced by prolonged exposures to hyperoxygenated air or to pure O_2 at atmospheric pressure.

Ozorio de Almeida (1934) found that one exposure to OHP rendered an animal

more susceptible to both the C.N.S. effects and the lung damage of OHP in subsequent exposures. In addition to lung pathology it was also reported that rats exposed to OHP showed atrophy of the testes, destruction of seminal epithelium and disappearance of all epididymis spermatozoa; the epididymis, seminal vesicles and the prostate, however, were unaffected. Numerous castration and basophilic cells were found in the anterior hypophysis. The histologic alterations were reported to be similar to those produced by radium or x-rays. The resulting sterility in the male was irreversible. The female rat was less profoundly affected than the male and the sterility induced was transient; pregnancy was not interrupted, and the growth of new-born rats was apparently normal. It was further pointed out that previously docile rats became combative and hyperexcitable after their exposure to OHP.

This change to belligerency and hyperexcitability following exposure to OHP was also observed by the reviewer (1940, unpublished data) but in addition to this it was found that these rats, and especially those which had suffered convulsive seizures, retained a pronounced motor dysfunction predominant in the forelegs, which persisted for months. A subsequent study of the phenomenon in a long series of animals (Bean and Siegfried, 1943) revealed that this condition can be regularly induced in both fore and hind limbs and the general body musculature by successive short exposures to OHP over a period of several days. In some animals this motor paralysis has been produced without the occurrence of convulsive seizures. The extent and degree of involvement depends not only on the intensity of the exposure, i.e., the duration, O_2 pressure, frequency and total number of successive exposures, but also on a rather striking individual variation in resistance and recovery. The fact that this condition has now persisted in survival animals for more than a year after the last exposure without significant abatement, is sufficient reason to believe that it is permanent.

The general features of this dysfunction, particularly the spastic nature of the paralysis, are highly suggestive of pathology involving the upper motor neurone. While the C.N.S. phase of oxygen poisoning may often appear to be "functional", as Smith (1899) maintained it was, there can be little doubt but that OHP acts on the C.N.S. in more than just a "functional" manner; it leaves a mark on the C.N.S. which persists for long periods and which may be made indelible, particularly with successive exposures. A systematic examination of the C.N.S. of animals in which this permanent motor dysfunction has been induced by OHP is in progress at the time of writing and while the evidence at hand does not as yet justify a final conclusion, the material obtained from preliminary experiments has shown definite pathology characterized as a "softening of the white matter" in the C.N.S. of animals in which this permanent motor dysfunction has been induced.

Turning to a consideration of the evidence of pathological action of OHP on the human organism, one finds it, naturally enough, less voluminous and less direct than that derived from animal experiments. Phillips (1931) reported that in the Davis Submersible Decompression Chamber "no evil effects, except subsequent sleepiness" were produced by exposures of men to O_2 at a pressure of 2

atmospheres; in one case functional albuminuria was prevented by such exposures.

Smith (1899) maintained that the autopsy findings in fatal cases of caisson sickness in men were so similar to those observed in his experimental animals poisoned by increased O_2 pressure as to justify the belief that O_2 poisoning contributed to the occurrence of caisson sickness. This view has found no very substantial support. Nevertheless, where the exposures to very high air pressures are prolonged, an involvement of an O_2 poisoning in compressed air illness is not only possible but very probable, particularly in view of the additive effects of CO_2, high tensions of N_2 and O_2, as discussed above (see section II). Furthermore the case reports of Shilling and Willgrube (1937) on divers who, having had attacks of caisson sickness, were placed in the recompression chamber and exposed to relatively high air pressure for considerable length of time, indicate that pulmonary pathology was induced by increased O_2 pressure. Jenkinson (1939) reported that at a pressure of 4 atmospheres O_2 is rapidly fatal.

The prediction voiced by Shilling and Adams (1933) that in men, recovery from O_2 convulsions would probably be rapid and complete, finds some substantiation in the work of Behnke, Johnson, Poppen and Motley (1935). These authors report that in human subjects complete recovery from the effects of breathing OHP (syncope, absence of radial pulse and convulsions) "followed immediately" the inhalation of air. On the basis of their experimental results these investigators were led to the opinion that "Healthy men between the ages of 22 and 40 can breathe pure oxygen with comparative safety as follows: 4 hours at 1 atmosphere; 3 hours at 2 atmospheres; 2 hours at 3 atmospheres." Substernal pain and dry cough, however, were observed as a result of some exposures; this was interpreted as indicative of lung irritation. The pulmonary changes, however, were considered "not impressive" and of minor importance in comparison with the changes referable to the nervous system. But the authors do suggest that incipient pulmonary changes at 3 atmospheres' pressure may have been responsible for the attendant leucocytosis even though symptoms of pulmonary irritation such as cough and pain in the chest were absent. One subject was unconscious for 20 minutes after the onset of convulsions; this could hardly be termed an "instant" or an "immediate" recovery which Shaw, Behnke and Messer (1934) have stressed is a characteristic feature of O_2 poisoning, and must represent a lag in tissue recovery.

In later experiments, Behnke, Forbes and Motley (1936) found a state of impending collapse in their subjects after 3 to 4 hours' exposure to O_2 at 3 atmospheres and although consciousness was retained, all of them looked dazed and gave indication of partial stupefaction. The authors conclude that healthy men can breathe O_2 at a pressure of 3 atmospheres (30 lbs. gauge) for 3 hours without distressing symptoms. In this connection the authors report a "gradual recovery" of from 20 to 60 minutes in the subjects on their return to air at atmospheric pressure; nausea and dizziness disappeared within a few minutes but the return to the normal of blood pressure, pulse rate, pupillary diameter, visual acuity and facial color occupied a "considerably longer time." End and Long

(1942) accept the interpretation that O_2 at a pressure of 3 atmospheres can be safely inhaled for 3 hours but believe that at 4 atmospheres O_2 is dangerous.

The symptomatic indications of damage induced in human lungs by exposure to OHP, "unimpressive" as they may be, cannot be dismissed as insignificant; this would appear to be especially so in view of the well-demonstrated pathology produced in experimental animals by such exposures and the observation that this pulmonary pathology develops gradually. The fact that an individual exposed to these adverse environmental conditions may manifest no striking reaction until a certain critical level of intensity or duration of exposure is reached, does not justify the assumption that his tissues remain entirely unaffected by anything short of that level. Actually an exposure carried to the critical level represents a breakdown test and it would be erroneous to maintain that no important changes occur except in those exposures which precipitate violent reactions and gross symptomatology of tissue damage. Autopsy examination might be surprisingly revealing.

Furthermore symptomatic recovery from the effects of OHP, while seemingly suggestive of an absence of pathology, may be misleading because of wide anatomical and physiological margins of safety. The possible dangers inherent in subsymptomatic exposures to OHP can not, therefore, be ignored. On the other hand it must be recognized that under certain exigencies the administration of OHP, like that of O_2 at atmospheric pressure, may not only be advisable, but may actually amount to a life-saving measure.

8. (a) *OHP in decompression from compressed air.* The use of OHP has found practical application in facilitating decompression of men from compressed air. Bert had reported that breathing a gas mixture high in O_2 content permitted decompression of animals with less danger of nitrogen bubble formation. About a quarter of a century later von Schrötter (1904) advocated that compressed air workers should breathe pure O_2 for five minutes in order to wash out the nitrogen dissolved in the tissues before decompression. But Ham and Hill (1905), finding cats were convulsed in six minutes by O_2 at pressures of 50 pounds, claimed it was ". . . unsafe to use Schrötter's method of 50 pounds and upwards. Below that pressure the risks of fatal air embolism are much less and the method is hardly worth employing." Hill and Greenwood (1907) were of the same opinion. Zuntz (1909) recognized the feasibility of using O_2 under increased pressure to aid in decompression as did Bornstein (1910). The early argument of Ham and Hill against the use of OHP in decompression of caisson workers was later changed following experiments of Twort and Hill (1912) on men, in which O_2 was breathed for 9 minutes at a pressure of 3 atmospheres and during the subsequent decompression to atmospheric pressure. It was concluded from these experiments that the nitrogen dissolved in the urine under compressed air is rapidly cleared out by breathing OHP and the authors state: "The practical application of these results to the prevention of caisson sickness is obvious." In more recent years many investigators have studied and recognized the advantages of using OHP in decompression (Hill, 1932; Shilling and Adams, 1933; Phillips (1931); Dorello, 1934; Davis, 1935; Behnke and Shaw, 1937; Jones et al., 1940; and others).

(b) *OHP in therapy.* There is good reason for supposing that OHP might be of distinct value for therapeutic purposes in some conditions. Obviously such use calls again for an evaluation of possible benefits to be derived, and the disadvantages and dangers to be encountered. One of the earliest attempts to use OHP therapeutically is that of Valenzuela (1887) who had found in preliminary animal experiments (rabbit) that exposure to O_2 at pressures as high as about two atmospheres (1520 mm. Hg) for an hour caused a fall in the body temperature from 38.4°C to 32.2°C. The general effect of such exposure was said to produce a torpor in the animals from which they recovered on decompression. He then studied the effects of OHP on febrile septicemia induced in a rabbit by the inoculation of "serous fluid with a putrid smell from a dead body." The temperature of septicemic animals treated by exposure to OHP (O_2 at pressures of 1.4 atmospheres for 2 hours) decreased 1.7°C. whereas in the controls without treatment it increased 3°C. After 3 successive exposures on 3 days the O_2 treated rabbit had recovered on the fourth day; the control was dead. Valenzuela then applied the same treatment to human subjects suffering from pneumonia and reported beneficial results.

Fischer and Andersen (1926a, b) demonstrated that the cells of some tumors were more susceptible to the destructive action of OHP than normal cells, but attempts to use this differential susceptibility to destroy tumors in vivo (Fischer, Andersen, Demuth and Laser, 1927) were not very successful. Of 158 tumorous mice exposed to O_2, 2 were completely cured and 3 were favorably affected; 68 of the animals, however, were killed by the O_2 treatment. In other work on this subject (Fischer, Andersen and Demuth, 1926) it was found that if copper or selenium were injected previous to the exposure to the O_2, the selective destruction of tumor cells was more pronounced.

Ozorio de Almeida (1934b) found that the selective destruction of tumor cells by OHP was enhanced by previously starving the animals; the starved animals became more resistant to the OHP whereas the tumor cells were completely destroyed. Basset et al. (1935) reported that mouse sarcoma 37, bathed in physiological saline, was destroyed by exposure to O_2 at a pressure of 1800 atmospheres for 30 minutes but at pressures of 1000 atmospheres it was not so affected. Campbell (1937) failed to obtain any satisfactory destruction of rat tumors by OHP. Attempts to use OHP in the treatment of malignancies in man by Auler, Herzogenroth and Wolff (1929) and by the South American investigators have not met with any notable degree of success. The treatment of leprosy by OHP has also been carried out in South American laboratories and while it appeared that the progress of the disease may have been somewhat slowed thereby, no cure resulted. Ozorio de Almeida and Pacheco (1941) employed OHP in therapeutic studies of experimental gas gangrene; Pacheco and Costa (1940; 1941) carried out experiments on the influence of OHP on clostridium welchi; de Mesquita (1941) reported cases of psoriasis treated by OHP.

One point in connection with the possible application of OHP to therapy which is deserving of special mention concerns the influence of CO_2. It is now well recognized, after repeated demonstration by various investigators that the

adverse effects of OHP are increased to a striking degree by the presence of CO_2. Other things being equal, then, one would expect that in those conditions in which there is an abnormal retention of CO_2 the adverse reactions to OHP might be unduly prominent. While it would seem that OHP should readily relieve hypo-oxemias, such for example as that resulting from extensive pulmonary pathology, such treatment might at the same time be complicated by the failure to concomitantly facilitate the removal of CO_2. It is not unlikely that some other types of acidosis might also augment the adverse effects of OHP.

(c) *OHP in CO poisoning.* The administration of O_2–CO_2 mixture for the resuscitation from carbon monoxide poisoning, long championed by Henderson, has proven of value, but the use of OHP in the treatment of such poisoning might seem to offer some further advantages. Haldane (1895) pointed out that the higher the tension of O_2 to which an animal is exposed the less dependent it is on its RBC's for oxygen, because of the increased amount of O_2 carried as simple solution in the plasma. The importance of this dissolved O_2 is further enhanced by the fact that the presence of CO in the blood so alters the O_2 dissociation curve of hemoglobin as to render that fraction of the hemoglobin which may still be functional, less effective in the carriage of O_2 than it otherwise would be. OHP should, then, be especially effective in preventing the anoxia in CO poisoning.

In addition to preventing anoxia in CO poisoning, the use of OHP would seem to provide further advantage in that it should be more effective in displacing carbon-monoxide from its combination with hemoglobin and this for two reasons: first, simply because at high concentrations O_2 can more readily compete with CO for hemoglobin: second, because the increased blood acidity obtaining in animals exposed to OHP (Bean, 1931) should, according to Stadie and Martin (1925), facilitate the removal of CO from the hemoglobin.

In experimental tests Haldane (1895) reported that OHP (O_2 at pressures of about 2 atmospheres) abolished the usual toxic action of even very high concentrations of CO. He further found that animals whose hemoglobin had been saturated with CO and whose lives had been maintained under those conditions by OHP, could be safely returned to the normal atmosphere if the CO were first washed out without permitting the O_2 pressure to fall below 2 atmospheres. These experiments were performed as part of an investigation of mine rescue methods, but no attempt seems to have been made at that time in their practical application to resuscitation from CO poisoning. The report of Schmidt-Kehl (1926) also points to the possible use of OHP for this purpose.

One reason for using CO_2 along with O_2 at atmospheric pressure in the treatment of CO poisoning is that it prevents an excessive alkalinization of respiratory control mechanisms which would otherwise occur as the result of the release of Na from lactate which had accumulated during the period of anoxia. Another advantage of the use of CO_2 is that it should, according to the findings of Stadie and Martin (1925), facilitate the removal of the CO from its combination with hemoglobin. Both of these arguments would appear to be applicable also to the use of OHP in the treatment of CO poisoning. But if, as has been observed (Bean and Haldi, 1932), the lactic acid is not as adequately removed in OHP as

under normal conditions, the release of Na from the lactate on the administration of OHP may be of less significance than in the case of O_2 administration at atmospheric pressure. On the whole the possible use of OHP in carbon-monoxide poisoning seemed to warrant further investigation. Experiments combining the administration of OHP and artificial respiration were therefore carried out by Doctor Bohr and the author (unpublished data, 1941) on rats. Circumstances prevented the completion of that study so that the data were insufficient to justify a final conclusion, but the results were suggestive of beneficial effects.

End and Long (1942) found that O_2 at pressures of about 30 pounds would resuscitate dogs and guinea pigs poisoned by carbon-monoxide even without artificial respiration. The curves representing the elimination of carbon-monoxide from the hemoglobin, however, became asymptotic with about 20 per cent of the hemoglobin still combined with CO; this "flattening out" was quite a constant finding and the authors suggest it may have been "due to the animals' habit of falling asleep.... The diminished respiration and more sluggish circulation incidental to sleep evidently retard elimination of carbon monoxide." It was proposed that OHP be used for resuscitation of human beings poisoned by CO.

(d) *OHP in shock.* Another condition in which the therapeutic use of OHP might conceivably be of benefit is that of shock. Following severe operative procedures, such as that of decerebellation which is occasionally attended by considerable loss of blood, it has been customary for the reviewer to subject the operated animal (pigeon and rat) to O_2 at pressures of about 2.5 atmospheres in short intermittent exposures. The apparent beneficial results derived from this treatment in tiding the animals over post-operative depressive states, augurs well for its possible success in the treatment of some cases of secondary shock. Frank and Fine (1943), however, report that exposure of experimental animals to O_2 at a pressure of 3 atmospheres did not favorably alter either the survival time or any of the commonly observed phenomena of shock, even in those animals (7 of 15) in which the O_2 concentration of venous blood was thereby maintained at normal levels by the OHP; these authors concluded that oxygen as a therapeutic agent in hemorrhagic shock is "of doubtful value."

In attempts to use OHP therapeutically in any of the conditions for which it might appear to promise advantages, its inherent dangers, already emphasized, must be recognized. Furthermore, in experimental studies, due cognizance must be taken of the fact that OHP, improperly employed may result in deleterious effects which may completely overshadow any possible benefits and lead to an unfair condemnation of a treatment which if administered with proper precaution might be of distinct value.

ETIOLOGY OF THE REACTIONS TO OXYGEN AT HIGH PRESSURE. Bringing together the various interpretations offered in explanation for the adverse effects induced by OHP calls for a consideration of the experimental conditions and procedures which led to the original conclusion that OHP was toxic and caused convulsions and death of animals exposed to it.

In his pressure studies, Bert analyzed the air of closed chambers in which birds

had succumbed as a result of the accumulation of their expired CO_2, an adequate O_2 tension having been provided either by the use of hyperoxygenated air or by ordinary air at moderately increased pressures. From the results of these experiments he concluded that death occurred when the CO_2 tension of the chamber air had risen to a relatively constant value, which for sparrows was about 26 (CO_2 percentage $\times$ pressure in atmospheres). It was observed, however, that sparrows exposed to higher pressures succumbed before the CO_2 tension had risen to the theoretically lethal level; in fact, for pressures above 3 atmospheres, the CO_2 tension in the chamber at the time of death progressively decreased, as the barometric pressure employed was increased. (See tables 5 and 6.) From this Bert concluded that death in these higher pressures could not have been caused

TABLE 5

1	2	3	4	5	6	7	8	9	10
NUMÉROS DES EXPÉRIENCES	PRESSION	DURÉE DE LA VIE	DURÉE DE LA VIE POUR UN LITRE D'AIR A 76 C	TENSION PRIMITIVE DE L'OXYGÈNE	COMPOSITION DE L'AIR MORTEL		$CO_2 \times P$	$O \times P$	$\frac{CO_2}{O}$
					CO_2	O			
	atm.	*h. m.*	*h. m.*						
CXXXII	2	3 49	3 4	41.8	12.6	3.2	25.2	6.4	0.72
CXXII	3	1 50	1	62.7	7.8	10.7	23.4	32.1	0.75
CXXVII	4	1 35	39	83.6	5.6	13.2	22.4	52.8	0.72
CXXIII	$5\frac{3}{4}$	1 30	27	120.1	3.8	15.5	21.8	89.1	0.70
CXXI	6	1 20	22	125.4	3.5	16	21.0	96	0.71
CXXVIII	8	1 38	20	167.2	2.4	16.8	19.2	134.4	0.60
CXXIV	9	1 10	14	188.1	2	17.5	18.0	157.5	0.59
CXXV	12	45	6	250.8	1.2	18.5	14.4	222.8	0.50
CXXX	12	45	1	250.8	1.3	18.7	15.6	224.4	0.59
CXXIX	14	45	1	292.6	0.9	18.5	12.6	263.2	0.43
CXXXI	14	39	4	292.6	0.9	18.5	13.2	263.2	0.43
CXXVI	15	39	1	313.5	0.8	19.4	11.2	291	0.53
CXXXIII	17	39	3	355.3	0.6	18.8	10.2	319.6	0.30
CXX	20	25	2	418.0	0.4	18.8	8	319.6	0.30

by the accumulating CO_2; and that it must, therefore, have been due to the increased O_2 tensions.

Certainly these particular data of Bert are highly suggestive that the increased O_2 tension was involved in the cause of death at the increased pressures and that O_2 at high pressures might, therefore, as he says, be considered a dangerous agent. But they would hardly seem to justify the conclusion that the increased O_2 by itself was the only lethal agent. At any rate our present knowledge of the interrelationship of CO_2 and high pressures of either air or O_2, does not permit the dismissal of the CO_2 tensions in these experiments of Bert as insignificant, even though some of them were far below his theoretically lethal constant. Nevertheless it was these data upon which Bert based his conclusion that while at moderately increased barometric pressure an accumulation of CO_2 in the pressure chamber might contribute to the death of the animals, at the higher pres-

sures death was caused exclusively by the increased O_2 tension alone. Speaking of the effects of ordinary air at increased pressure in a chamber without either ventilation or CO_2 absorption, Bert says: "Pour les pressions très-élevées, la mort est due exclusivement à la tension trop considérable de l'oxygene ambiant."

Bert experienced considerable difficulty, as he confesses, in devising suitable means for removing CO_2 from the compression chamber of his sparrow experiments. This, together with his earlier conclusions regarding the lethal CO_2 tension, may help to explain why he seemingly dismissed the removal of CO_2 from respired air as unimportant. He did, however, perform a few experiments

TABLE 6

1	2	3	4	5	6	7	8	9	10
NUMÉROS DES EXPÉRIENCES	PRESSION BAROMÉTRIQUE	TENSION D'OXYGÈNE DANS LE MÉLANGE PRIMITIF	QUANTITÉS CORRESPONDANTES D'ATMOSPHÈRES D'AIR	DURÉE DE LA VIE	DURÉE DE LA VIE POUR UN LITRE D'AIR A 76 C	COMPOSITION DE L'AIR MORTEL		$CO_2 \times P$	PHÉNOMÈNES GÉNÉRAUX PRÉSENTÉS PAR LES ANÍMAUX
						CO_2	O		
	atm.		*atm.*	*h. m.*	*h. m.*				
CXLIII	1.25	32.5	1.5	1 30	1 36	22.1	3.5	27.6	Pas de suffusions crâniennes
CXLIV	1.5	69.0	3.3	1 30	1 36	16.7	28.6	25.1	Pointillé rouge au crâne
CXLVI	2.5	115.5	5.5	3	53	11.1	33.3	27.7	Suffusions crâniennes
CXL	2.0	117.6	5.6	3	52	13.4	44.4	26.8	Suffusions crâniennes
CXXXIX	1.75	146.3	7.3	2 20	31	11.9	67.8	20.8	Suffusions crâniennes
CXXXVIII	3.0	258.0	12.1	1 15	10	5.6	78.9	16.8	Suffusions crâniennes
CXLI	4.0	501.6	14.4	1	7	2.1	71.1	8.4	Convulsions, suffusions
CXXXVII	5.0	415.0	19.7	1 20	6	1.4	80.5	7.0	Convulsions, suffusions
CXLII	8.5	433.5	20.7	20	2	0.8	47.8	6.8	Convulsions, suffusions
CXLV	5.5	467.5	22.3	20	1	1.0	82.5	5.5	Convulsions, suffusions

on birds in which the CO_2 was removed by partially filling the compression chamber with a potash solution. In these experiments, in which he says all trace of CO_2 was removed from the chamber, the death of those birds which did not succumb because of a depletion of the O_2, was assumed to have been caused by the toxic action of the increased O_2 tension of the highly compressed air. But such an assumption of an unadulterated O_2 effect cannot be accepted without some reservation; the very high barometric pressure of air employed must certainly have introduced complicating factors not attributable to the increased O_2 tension by itself.

As one reviews Bert's experimental protocols he becomes increasingly impressed with the apparent disregard which that investigator had for factors we now know are exceedingly important variables in, if not determinants of, the

response to increased pressures. This apparent disregard is perhaps best summed up in his statement to the effect that all the influences which changes in barometric pressure may exert on animals are due either to an insufficiency or to an excess of O_2 tension (*"Pas assez d'oxygène, en tension, ou trop d'oxygène, toute l'influence que les modifications barometriques excercent sur les animaux se résume en ces termes"*). His experiments on oxygen poisoning in dogs bear witness to the strength of his conviction on this point and deserve special mention.

These experiments were, with few exceptions, carried out as rebreathing procedures in which no attempt was made to absorb the expired CO_2 accumulating in the relatively small rebreathing balloon. In the majority of these experiments the CO_2 of the gas mixture breathed at increased pressure was between 8 and 10 per cent, the lowest figure given for this type of procedure was 5.4 and in one case it reached the astounding value of 12.9 per cent (at 6.75 atmospheres, the pressure used in that particular experiment, this would represent a tension of 87 per cent of one atmosphere). For those few experiments in which attempts were made to remove the CO_2 by pieces of potash placed in the bottom of a bottle, or by potash solution in the rebreathing balloon, no CO_2 analyses of the gas rebreathed are given. This removal of the CO_2 was, he insisted, quite unnecessary for the reasons presented above.

In addition to this matter of CO_2, Bert's experiments on dogs are open to question on another score, to which brief reference has already been made, viz., that of the very rapid decompression rates which were used. In spite of the fact that the pressures employed were as high as 8 atmospheres, and that the O_2 content of the compression medium was as low as 60 per cent, the decompression was often abrupt. Such procedures must have frequently resulted in O_2 and N_2 emboli which in themselves might well precipitate convulsive seizures and significantly enough the convulsions in Bert's dogs occurred during or following decompression. These seizures in dogs, described by Bert as O_2 convulsions were as Hill and Macleod (1903c) pointed out "clearly decompression results, and due to the effervescence of oxygen gas in the central nervous system."

In summary then it may be said that, important as the investigations of Bert were in that they drew attention to a new feature of the adverse effects of increased tensions of O_2, the experimental results which he details as representing the toxic action of OHP alone, are open to serious criticism on at least three main counts: first, because of the gross failure to recognize the possible importance of very high CO_2 tensions in the gas mixtures used; second, because of the frequent employment of very high barometric pressures of air or of high N_2 percentage mixtures in order to attain the desired increase in O_2 tension; third, because of the very rapid decompression employed. In considering Bert's views then it may be well to keep in mind that many of the reactions he described as those of O_2 poisoning involve more than the effects of O_2 alone. The fact that in spite of Bert's intentional disregard of these complicating experimental conditions, his observations have on the whole been confirmed by subsequent investigations which are not open to these criticisms, is more than of passing interest for it points to the possible significance of etiological factors discussed below.

A consideration of the accumulated data, including that of Bert, provides abundant evidence for concluding that the effects of exposure to OHP are generalized and involve many if not all tissues of the body and cannot, therefore, be legitimately localized to any one single or even several tissues, to the exclusion of others. But the outstanding features of the manifestations of those effects are predominantly those of respiratory difficulty, motor disturbances which frequently, though not invariably, include convulsive attacks, and eventual death. These features have directed attention to the lungs and to the C.N.S. which have been considered as organs for which the adverse action of OHP has an especial predilection and constitute the background for Smith's conclusion (1899) that the cause of the reactions to OHP are (1) pulmonary pathology and (2) an involvement of the C.N.S. If the proviso of admitting certain qualifications be permitted no strenuous opposition can be reasonably voiced against this interpretation so far as it goes and it provides a basis upon which the more intimate etiology of the responses to OHP may be discussed.

1. *Pulmonary Pathology as an Etiological Factor.* Thompson (1889) observing extensive pulmonary pathology in animals which had been exposed to OHP and had suffered convulsions therein, proposed that such pathology was an important contributor to the convulsive seizures. Smith (1899) finding dyspnea a prominent reaction in exposures to OHP, and at autopsy, severe pulmonary damage and pneumonia, was led to the belief that such pulmonary damage constituted a separate and a more slowly developing phase of O_2 poisoning than that of C.N.S. involvement, and that while this pathology might tend to postpone the C.N.S. effects of OHP by slowing up the O_2 absorption, it ultimately caused death of the animal.

Extensive pulmonary pathology might conceivably contribute to the reactions in animals exposed to OHP in two ways: 1, by preventing O_2 absorption and thus leading to an hypo-oxemia; or 2, by interfering with the elimination of CO_2. Where the increased O_2 pressure is very little above that of one atmosphere both of these conditions develop after prolonged exposures and the situation is the same as that when breathing hyperoxygenated air or pure O_2 at atmospheric pressure for prolonged periods; so far as the tissues beyond the lungs are concerned the condition may be then essentially one of low, rather than increased, O_2 tension as discussed above in section I. However, where the O_2 pressure is in excess of several atmospheres the condition of hypo-oxemia would not be likely to occur so long as the pressure was maintained. On the other hand, if the pathology be at all extensive as it frequently is, there would be an interference with the removal of CO_2. This might be partially compensated for by the establishment of a new diffusion gradient through hyperpnea and the elevation of blood pCO_2 so that with the attainment of a new steady state the elimination of CO_2 might not be appreciably decreased as has been repeatedly demonstrated. But because even a relatively small increase in CO_2 tension assumes a peculiarly high potency when associated with OHP any interference with the normal CO_2 removal at the lung cannot be dismissed as insignificant. This is particularly so because the enhanced reactions ensuing from the addition of small amounts of

exogenous CO_2 to OHP cannot be distinguished qualitatively from those induced by OHP in the absence of exogenous CO_2.

Stadie, Riggs and Haugaard (1944) dismiss the possibility that in exposures to OHP there is any retention of CO_2 in the blood or tissues such as is observed in other types of pulmonary pathology. In support of this opinion they cite the report of Behnke et al. (1934) that the arterial pCO_2 was not increased in animals exposed to OHP. Now if the exposure to OHP be such as to induce no pulmonary pathology—and as already pointed out this is not infrequently the case—there would, of course be no reason to expect that CO_2 elimination at the lungs would be very appreciably interfered with at pressures of 3 to 4 atmospheres; in fact its elimination might be facilitated under such conditions because of the hyperpnea which almost invariably occurs. Furthermore, one might by definition even rule out pulmonary pathology as a part of poisoning by OHP, since the typical reactions to OHP do occur in the absence of any demonstrable pathology, and in that case retention of CO_2 because of disturbed elimination of CO_2 at the lungs would also be ruled out. However, if pulmonary pathology be admitted as a part of the picture, the very extensive and severe lung damage frequently observed by so many investigators (see section on pathology) must, just as many other types of pulmonary pathology, lead to a retention of CO_2.

The importance of pulmonary pathology induced by exposure of animals to OHP was early impressed upon the reviewer performing experiments in which the effects of OHP on blood acidity, uncomplicated by this pulmonary pathology, were under study. The observations then and since have led to the conviction that in sacrifice experiments on animals exposed to OHP an inspection of the lungs for at least gross pathology should be made in the interpretation of results.

The mode of action by which OHP induces pulmonary pathology has not been clearly demonstrated. The more general view has been that OHP acts as an irritant directly on the pulmonary tissue. Ozorio de Almeida (1934) has interpreted the pulmonary pathology as a secondary result of diminished oxidations. Still another interpretation which has been offered is that it is secondary to circulatory effects of OHP, particularly on the right side of the heart. This last view is reminiscent of the explanation offered by Karsner for the pulmonary changes found in animals exposed to O_2 at atmospheric pressure.

In summary then one may conclude that the pulmonary pathology induced by OHP does contribute while the animals are under the increased pressure to the reactions referred to as those of poisoning by OHP. This contribution is to be attributed to the interference with the normal removal of CO_2. During decompression and in the post decompressional period, those reactions which represent a persistence of the toxic effects of OHP induced during the maintenance of the increased pressure are further complicated by the pulmonary pathology which, with the animal's return to normal pressure conditions, results in hypo-oxemia. But the fact that respiratory reactions, blood changes, convulsive seizures and death commonly occur in animals exposed to OHP in the absence of any demonstrable pulmonary pathology (Bert, 1878; Thompson, 1889; Smith, 1899; Born-

stein and Stroink, 1912; Bean, 1929; 1931; Shilling and Adams, 1933) indicates that while pulmonary pathology induced by OHP is, when present, contributory, it is not essential to the induction of those reactions typical of poisoning by OHP.

2. *The C.N.S. as the Site of Origin of the Reactions to Oxygen at High Pressure.* Bert concluded that the origin of the more pronounced reactions to OHP, particularly the convulsive seizures, was the C.N.S. This conclusion was based on several observations: the relief of the seizures by chloroform anesthesia, the relaxation of convulsively contracted muscles by section of their motor nerves and the retention of the excitability of striated muscle to direct stimulation after their reflex excitability had been lost. Significantly enough convulsive seizures did not occur either in air at pressures much below 19 atmospheres or in O_2 at pressures below about 3.5 atmospheres, that is to say, at pressures less than those necessary for the solution of 10 volumes percent of O_2 in the plasma over and above the normal 20 volumes per cent held in combination with the hemoglobin.

It was this greater solution of the O_2 in the plasma consequent upon exposure to high tensions of O_2 which Bert maintained was a toxic agent for the C.N.S., so that when the O_2 in the blood rose to about 35 volumes per cent it was rapidly fatal. "In mammals," he says, "trouble rapidly occurs only when the hemoglobin is saturated with oxygen and this gas enters the tissues from a state of simple solution." And "Whatever the explanation, it seems that for oxidation the tissues need borrowed oxygen, taken away from the oxyhemoglobin"—a comment especially apropos the importance and the carriage of CO_2 by the blood in O_2 poisoning discussed below. Because the convulsions continued after the pressure had been lowered, Bert contended that the real cause was some chemical change which, outlasting the apparent cause, continued to excite nervous tissue. That O_2 at increased barometric pressure acts on the C.N.S. has been accepted by all subsequent investigators whose experimental data represent more truly the effects of OHP than do those of Bert. Williams and Beecher (1944) noted in Drosophila that the maintenance of balance and equilibrium was the first attribute to be permanently lost and were of the opinion that the primary effect of OHP in these forms was on the nervous system.

Shilling and Adams (1933) reported that extensive microscopic studies of nervous tissue in brains of animals subjected to O_2 convulsions were made by Finley but that "the findings were essentially negative." Similarly Fahr (1941) recognizing that the symptoms of poisoning by OHP pointed to the C.N.S. as the site of involvement made special microscopic studies of the C.N.S. but no significant pathology was found there. The question arises as to whether the animals in these investigations may not have been sacrificed before degenerative changes could be demonstrated by the usual techniques.

Whether OHP itself operates directly on the C.N.S., or through the production of some intermediary toxic substance, or through a disturbed metabolism and removal of metabolites, or through a combination of these acting on peripheral as well as central structures, the permanently crippling motor dysfunction induced in rats by their repeated exposure to OHP (Bean and Siegfried, 1943) con-

stitutes conclusive evidence that OHP can cause permanent damage to the C.N.S. and that therefore its influence is not entirely functional, as has heretofore been widely held. Recent work reveals degenerative changes in the C.N.S.

3. *Carbon Dioxide as An Etiological Factor.* Although as already pointed out Bert dismissed CO_2 as of no consequence in the production of the reaction to O_2 at high pressure, an examination of his experimental protocols and data leaves no doubt but that CO_2 must have played a very large rôle in the response which he referred to as that of O_2 poisoning. The inverse relationship between the CO_2 and O_2 tensions in the lethal gas mixtures at various barometric pressures, shown above in tables 5 and 6, which formed the basis for Bert's conclusion that at high pressures the O_2 alone is responsible for the reaction, falls far short of ruling out CO_2 as an etiological factor. Indeed it would appear to be one of the earliest demonstrations of the now well recognized fact that tensions of CO_2 which at normal atmospheric pressure are too small to exert any very obvious effect, become highly and increasingly noxious when associated with an increased air or O_2 pressure.

The exceedingly high CO_2 content (as much as 12.9 per cent) of the gas mixture to which Bert's dogs were exposed has been mentioned above and, as would be expected, the blood of these animals showed a proportionately high CO_2 content. In one experiment, for example, the analysis of carotid blood in a dog when breathing air at normal pressure was: CO_2 22.3, O_2 17.2 volumes per cent; but when breathing hyperoxygenated air (74 per cent O_2, 10 per cent CO_2) at 7.25 atmospheres pressure, the blood CO_2 had risen to 72.3 and the O_2 to 30.1 volumes per cent. In another experiment the blood CO_2 rose from 24.0 volumes per cent in air at normal pressure, to 92.5 volumes per cent in hyperoxygenated air at 6.75 atmospheres.

The blood gas analysis figures for Bert's experiments in which potash was used to absorb the expired CO_2, are even more significant; in one such experiment with the animal in air at normal pressure the blood CO_2 was 20.9 and the O_2, 19.8 volumes per cent; in hyperoxygenated air (88 per cent O_2) at normal pressure the blood CO_2 was 34.5 and the O_2, 20.9 volumes per cent, but at 6 atmospheres' pressure the CO_2 had risen to 63.5 and the O_2 to 26.3 volumes per cent. Increases in the CO_2 content of the blood such as these are significant. Hill and Macleod (1903c) point out that Bert's animals "must have been rendered comatose with CO_2." Because Bert stated that at moderately increased O_2 pressures, the increase of CO_2 in the chamber did contribute to the adverse effects and death of the experimental subjects, his conclusion that CO_2 was of no consequence at higher O_2 pressures, is the more surprising.

Although Thompson (1889) indicated that the cause of the convulsions was undecided, he proposed that an accumulation of CO_2 in the body as a result of an interference with normal diffusion processes was responsible. "If the pressure of the inhaled atmosphere," he said, "be it oxygen or common air, is greatly increased, it is more difficult, and it requires more time for the CO_2 to diffuse from the blood into the air-vesicles, and from the air-vesicles into the tidal air in the wider portions of the air-passages. As a result, the CO_2 tends to accumulate in

the blood." Hill and Macleod (1903c) likewise claimed the diffusion of CO_2 in the lungs was impeded in compressed gases.

Evidence that CO_2 might somehow be related to the action of O_2 is found in the observation of Snell (1896) who maintained that an increase in CO_2 from 0.045 to 0.1 per cent in caissons was the forerunner of much illness. Moir (1895) was of the same opinion and suggested that the air be washed free of all CO_2 before it is pumped down to the men working in compressed air. Singstad (1936) recognizes the importance of CO_2 in compressed air and maintains that the difficulty in breathing experienced by some divers at the greater depths is caused by excessive carbon dioxide in the helmet as a result of insufficient ventilation. The report of Yamada (1918) also points to the significance of CO_2 in relation to the effects of O_2; he observed that 3 per cent CO_2 in room air, if administered continuously to man, caused an hyperpnea which gradually decreased, but when that same concentration of CO_2 was administered in pure O_2 the hyperpnea increased.

Gesell (1923), in his study of the factors which contribute to the regulation of respiration through their influence on the intracellular acidity of the respiratory centers, pointed out that a failure of reduction of oxyhemoglobin should interfere with the normal function of the hemoglobin in the transport of CO_2 from the tissues by the blood; this would lead to an accumulation of CO_2 in the respiratory centers and a consequent increase in breathing. Such a failure in the reduction of oxyhemoglobin should theoretically take place when an animal is exposed to pure oxygen at pressures of about 3 atmospheres and above, for under that pressure the amount of O_2 taken up by blood in simple solution would, according to physical laws, be more than sufficient to meet ordinary tissue requirements thus leaving the hemoglobin still fully saturated with O_2. The base normally provided by the reduction of oxyhemoglobin, and which normally serves for the transport of the greater part of the CO_2, would under such circumstances be missing and there should then follow, as a result, an undue accumulation of CO_2 in the tissues. Gesell found that the addition of CO_2 (5 per cent) to OHP (2700 mm. Hg) caused rapid deterioration and death of rats in about one half hour, whereas exposure to either OHP (2700 mm. Hg) without the CO_2, or to a mixture of O_2 (300 mm. Hg) and N_2 (2400 mm. Hg) with the addition of CO_2 (5 per cent) produced little more than hyperpnea and restlessness. This enhancement of effects by the combination of CO_2 with OHP was interpreted as evidence of an increased sensitivity of the organism to CO_2 as a result of the disturbed transport of CO_2. But CO_2 also augments the toxic action of OHP on organisms devoid of hemoglobin, as observed in some micro-organisms, and Williams and Beecher (1944) have shown that while Drosophila can withstand prolonged exposure to high CO_2 tensions at atmospheric pressure (15 per cent) they are peculiarly sensitive to the presence of CO_2 in the exposures to OHP. The authors state that CO_2 facilitates the toxic action of OHP so that "the rate of poisoning can be described as a linear function of carbon dioxide tension."

According to the disturbed CO_2 transport theory the effects of exposure to OHP should begin to be pronounced when the O_2 tension reaches an equivalent of 3 atmospheres. Interestingly enough, the experiments of Bert (1878), Thomp-

son (1889), Smith (1899) and of subsequent investigators do show this to be true. Bert found that convulsions did not occur until the O_2 tension of the compressed gas was somewhat in excess of 3 atmospheres, and that in those animals which succumbed, the blood during the exposure contained about 10 volumes per cent of O_2 in simple solution in addition to the 20 volumes per cent combined with the hemoglobin. Under such conditions the oxyhemoglobin could not have been reduced and the animal must therefore have been deprived of one of its most important mechanisms of CO_2 transport with the result of a partial damming back of CO_2 in the tissues.

Bert pointed out that in O_2 poisoning the oxyhemoglobin did not give up its O_2 and his statement to the effect that for oxidation the tissues need borrowed oxygen, taken away from the hemoglobin, indicates that he had some notion that the failure of the oxyhemoglobin to give up its O_2 might be an important factor in O_2 poisoning. He says, "Or, fait du plus haut intérêt, c'est en présence de cet oxygène simplement dissous, libre, que les oxydations intimes se ralentissent, puis s'arrêtent. Il semble que les tissus aient besoin, pour s'oxyder, de l'oxygène emprunté, enlevé à la combinaison oxyhémoglobique, si bien que, en présence de l'oxygène dissous apporté par la compression, ou les tissus deviennent incapables d'opérer cette dissociation, ou les globules ne peuvent plus céder leur oxygène, et demeurent condamnés à la saturation perpétuelle." The decreased oxidation of which Bert speaks has been generally confirmed and is discussed more fully below, but one suggested explanation, which may be mentioned to advantage here is that it may be a secondary effect of the increased tissue acidity arising from a disturbed CO_2 transport.

In order to test this theory of hemoglobin involvement in O_2 poisoning a number of studies were carried out (Bean, 1929, 1931) among which were those on blood acidity; for if OHP disturbs the carriage of CO_2 by the blood and causes a rise in tissue CO_2, these changes should be reflected in an alteration in blood pH. The changes in blood acidity of dogs exposed to OHP were therefore determined by continuous electrometric methods. The results showed that in those animals exposed to OHP for periods short of the convulsive stage, there occurred an increase in the acidity of both arterial and venous blood (pH changes of from 0.05 to 0.19) when the O_2 pressure was increased to more than 3 atmospheres. Since, in these exposures the acid change was reversed on decompression it could not be attributed to lung damage, and under these conditions provides substantial evidence that the CO_2 transport of the blood is disturbed by OHP. Such disturbance, resulting in an increased CO_2 in the tissues, particularly those intimately associated with the regulation of breathing, provides an explanation for the hyperpnea and dyspnea which accompanied these exposures and which are characteristic findings in exposures of animals to OHP.

The observation in these same experiments that the elevation of blood acidity was less pronounced in those animals which were particularly hyperpneic during the exposure to OHP is worthy of note for it indicates that the increased acidity may be partially compensated by an increased breathing. Another compensatory mechanism suggested by these experiments is an increase in the volume flow of blood, although the recorded increase was only slight.

The continuous observation of the circulating venous blood in these experiments revealed that it remained in a highly oxygenated state (colour determination) throughout the exposure to OHP; withdrawn samples frothed copiously, indicating an O_2 supersaturation. This proves unequivocally that under such O_2 pressures the oxyhemoglobin is not reduced and it follows that CO_2 transport must, as a result, be affected. The data, then, provide corroborating evidence that the acid change in the blood is to be explained on the basis of a disturbed CO_2 transport, and an accumulation of CO_2 in the tissues.

The experiments of Campbell (1929) provide perhaps even more direct evidence of an accumulation of CO_2 in the tissues of animals exposed to OHP. Nitrogen was injected intraperitoneally and subcutaneously into rabbits which were then exposed to OHP. Analyses of the gas withdrawn from these artificial gas pockets of animals exposed to O_2 at a pressure of 2639 mm. Hg (3.5 atms.) showed that the CO_2 tension, as also that of the O_2, was markedly increased (average over 100 per cent) as compared with that from animals which were exposed to air in which the partial pressure of O_2 was only 562 mm. Hg. It was believed that the CO_2 tension of the tissues was actually higher than that of the gas pockets. In those animals which succumbed to the increased O_2 pressure the CO_2 tension was distinctly higher than that of the survivors; "in four out of five animals the CO_2 tension was 213 mm. Hg (30 per cent) or more." Campbell points out that this accumulation of CO_2 may be the cause of the narcosis and convulsions of O_2 poisoning but suggests that the explanation of the increased CO_2 may be a vasoconstrictive effect of O_2 (Campbell and Hill, 1931).

Hill (1933) cites Campbell's results as indicative of a disturbed CO_2 transport arising from the failure in the reduction of the oxyhemoglobin. In his own experiments Hill found that a preliminary 15 minute exposure to a mixture of 5 per cent CO_2 and 95 per cent O_2 at atmospheric pressure lowered the critical pressure at which convulsions occurred when the animals were subsequently exposed to OHP. The onset of convulsions was also found to be accelerated by CO_2; a monkey showed no symptoms of O_2 poisoning in a 30 minute exposure to O_2 at a pressure of 4.7 atmospheres but after a preliminary exposure to 5 per cent CO_2 and 95 per cent O_2 at atmospheric pressure, convulsions came on 13 minutes after raising the pressure with O_2 to 4 atmospheres. Similar results were obtained in experiments on rats, guinea pigs and goats. It is of special interest that this effect of CO_2 should be evident even when the animal was shifted to OHP which was free from CO_2; a goat which showed no symptoms in a 27 minute exposure to O_2 at 4 atmospheres was subsequently subjected for a few minutes to 22 per cent CO_2 in air at atmospheric pressure after which the chamber was washed out with O_2 and the pressure raised to 3.7 atmospheres. Convulsions then came on in 7 minutes. Hill concluded that "increase of carbon-dioxide tension in the tissues is a factor in the production of convulsions, which follow exposure to high pressures of oxygen." Massart (1934) has likewise observed that in the presence of CO_2 the onset of convulsive seizures was accelerated.

Behnke, Shaw, Shilling, Thompson and Messer (1934) having found that the average CO_2 tension of mixed venous blood of dogs breathing O_2 at a pressure of 4 atmospheres was only 6.5 mm. Hg higher and the pH only 0.03 unit lower

(the latter by indirect methods) than that found during exposures to air at 1 atmosphere, thought no significance should be attached to such small CO_2 changes and stated: "It seems highly improbable that the rise in carbon-dioxide tension due to the absence of reduction of the oxyhemoglobin, and the resultant increase in acidity is sufficient to account for the symptoms of oxygen poisoning." In later work, however, Shaw, Behnke and Messer (1934) agreed that "Carbon dioxide tensions which are wholly innocuous when associated with oxygen pressures of less than 1 atmosphere, prove highly toxic when associated with oxygen at 4 atmospheres of pressure"; and Behnke and Willmon (1939) state that increased acidity of venous blood (0.03 pH) is "worthy of emphasis" (see below).

Shaw, Behnke and Messer (1934) reported that symptoms of O_2 poisoning occurred in anesthetized (barbiturate) dogs breathing OHP for prolonged periods, even when alveolar CO_2 content was maintained at subnormal levels by artificial overventilation; from this it was concluded that CO_2 could not have been the cause of the reaction to OHP. Now artificial overventilation should, of course, tend to lower tissue CO_2, but this, it would appear, does not justify their conclusion which is based on the erroneous assumption that tissue CO_2 and alveolar CO_2 always run parallel courses. Obviously any breakdown in the system which transports metabolites from the tissues to the lungs should result, other things remaining constant, not only in an accumulation of those metabolites at their sites of origin in the tissues, but also, and consequently, in a diminution in their concentration at the pulmonary terminal of the transport system. Indeed, barring the factors of compressional inflow and increased diffusion resistance, one would expect to find a subnormal CO_2 content in the alveolar air of animals exposed to OHP even without artificial overventilation for several reasons—viz., an inadequate carriage of CO_2 from the tissues to the lungs; slowed diffusion through damaged alveolar membranes; the blowing off of alveolar CO_2 by the hyperpnea which commonly occurs in O_2 poisoning; and a diminished tissue metabolism.

These authors (Shaw, Behnke and Messer, 1934) do, however, recognize CO_2 as a contributing cause in oxygen poisoning but believe that its influence "is to render the oxygen more toxic or the tissues more sensitive to the effects of oxygen." On the other hand, Behnke, Johnson, Poppen and Motley (1935) suggest that exposure to O_2 at atmospheric pressure increases the sensitivity of nervous tissue to CO_2, as had Yamada (1918).

Massart (1934) has maintained that the augmentation of response to OHP which occurs on the addition of small amounts of CO_2 to the respired gas is caused by an increased uptake of O_2 consequent upon the hypercapneic hyperpnea. Anything which increases breathing tends, he says, to hasten the onset of convulsions whereas a decrease in ventilation postpones the onset. The less pronounced elevation in blood acidity in those animals which were markedly hyperpneic (Bean, 1931) point to an opposite conclusion. In order further to evaluate hyperpnea as a possible contributor to O_2 poisoning, Bohr and Bean (1942a) subjected tracheotomized, urethanized or decerebrate rats to controlled artificial respiration in O_2 at pressures of 6 atmospheres; the results of such experiments showed, contrary to Massart's contention, that artificial hyperventila-

tion postponed, rather than hastened the onset of reaction to OHP. This postponement of the onset of the toxic action of OHP might very well be explained on the basis of an improved CO_2 diffusion gradient from the plasma to the alveolar gas as a result of the hyperventilation. These experimental data point again to the importance of CO_2 and its disturbed transport in poisoning by OHP.

It is conceivable that CO_2, whether it be of exogenous or endogenous origin, might accelerate the onset and augment the reaction to OHP by virtue of its recognized vasodilating action, since an increased blood flow should accelerate the O_2 saturation of the tissues. On the other hand, vasodilatation with a consequent increase in blood flow should, as already pointed out, tend to maintain the removal of endogenous CO_2 and so partially compensate for the disturbed CO_2 transport by hemoglobin; vasodilatation might then postpone or alleviate the response to OHP. But in any case CO_2 must certainly play a more important rôle than simply one of vasodilatation.

Stadie, Riggs and Haugaard (1944) in reviewing the subject state "there is clear evidence that the *partial pressure* of carbon dioxide in the tissues is *increased* by high oxygen," but maintain that this increase is not due to a retention of CO_2, such as might occur, for example, in certain types of pulmonary pathology. They are of the opinion that the failure in the reduction of oxyhemoglobin provides "sufficient explanation" for the increased CO_2 partial pressure of the tissues.

A careful theoretical analysis by Stadie, Riggs and Haugaard (1944) of the possible rôle which oxyhemoglobin and its non reduction might play in oxygen poisoning, led them to conclude that "the changes in the blood expected on physico-chemical grounds do occur when oxygen excess is inhaled." On the other hand they cite the failure of Behnke et al. (1934) to find an increase in the arterial CO_2 tension, as proof that there is no interference with the transport of CO_2. But, provided CO_2 elimination at pulmonary membranes and ventilation are not diminished, why should one select an increased arterial CO_2 tension as an infallible index of a disturbance in the transport of CO_2 from the tissues to the lungs? The hyperpnea which commonly occurs in OHP might lead one to expect a decrease in arterial CO_2 tension, rather than an increase. To use a rough analogy, the emptiness of trucks on their return trip is not proof of the adequacy of a transport system.

If there is no "retention" of CO_2, and if there is no disturbed transport of CO_2 from the tissues, and if further, as is agreed, there is no increase in the production of CO_2 in the tissues, how is the increased tension of CO_2 in the tissues, for which there is "clear evidence," to be explained? Stadie and associates accept the 1934 interpretation of Behnke et al. that the non reduction of oxyhemoglobin and the increase in CO_2 tension, play no significant part in the poisoning by OHP—an interpretation which as indicated above, was later modified (Shaw, Behnke and Messer, 1934) to include CO_2 as a contributing cause of O_2 poisoning. This acceptance was based for the most part on three arguments, one of which was, that "the symptoms of CO_2 acidosis do not resemble remotely those of oxygen poisoning." But why should one expect that the response to CO_2 in association with OHP to be the same as that of CO_2 at atmospheric pressure?

Certainly the experimental conditions upon which the CO_2 is superimposed in each of these two situations are not comparable.

If it be assumed that CO_2 is not causally involved in the reactions to OHP, and if as stated, the reactions to OHP are so remotely different from those induced by CO_2, we should expect that in the administration of CO_2 to animals exposed to OHP, some of the distinctive CO_2 effects would retain their identity in the animals' reaction to such conditions. But as a matter of fact, all reports indicate that the addition of CO_2 results, not in any new type of response, but rather, in simply an accelerated precipitation and enhancement of the same responses which are typical of OHP in the absence of the exogenous CO_2. The similarity of the OHP and CO_2 effects is attested to by the statement of Shaw, Behnke and Messer (1934) that the rôle which CO_2 plays "is to render the oxygen more toxic or the tissues more sensitive to the effects of oxygen."

A second reason for dismissing the non-reduction of oxyhemoglobin and the increased CO_2 tension, was that "the changes observed were slight." But it should be pointed out that those same changes which were originally considered slight and of no consequence have more recently been re-evaluated in the light of new experiments and are now spoken of as "worthy of emphasis" (see below).

The third argument for dismissing the factors of disturbed transport and increased tension of CO_2 was the generally recognized fact that the maximal response to OHP does not occur at that O_2 pressure which is just sufficient to maintain the hemoglobin in a constant state of O_2 saturation; much more pronounced effects are induced at higher O_2 pressures. This is of course one line of evidence that there are other factors than the non-reduction of oxyhemoglobin involved in poisoning by OHP but it does not, in the opinion of the reviewer, rule out the increased CO_2 tension arising from such non-reduction as one of the causative agents.

The argument that hemoglobin involvement in poisoning by OHP is of no consequence because some organisms devoid of this pigment are more readily killed by OHP than are those whose life is dependent upon it, would appear to be invalid: for there are on the other hand numerous organisms not possessed of hemoglobin which are strikingly resistant to the toxic action of OHP, the resistance of Drosophila (Williams and Beecher, 1944) for example is much greater than that of mice, and this might suggest that hemoglobin is after all an important contributor to the greater susceptibility of higher forms to the toxic action of OHP.

In summary then it may be said that the evidence clearly shows that in exposures to OHP there is an increase in the CO_2 tension of the tissues; that there is a non reduction of the oxyhemoglobin and that this, in the absence of other changes, provides sufficient explanation for the increased tissue CO_2 tension. The denial of the importance of the increased CO_2 tension as a causative factor in poisoning by OHP, based chiefly on the early report of some investigators that this increase was too slight (a view later modified in light of later experiments) appears to be untenable because of the now well accepted fact that an increase in CO_2, of otherwise inconsequential magnitude, becomes highly potent in the

presence of OHP. This increased potency is manifest by a pronounced enhancement of those reactions typical of OHP in the absence of exogenous CO_2; an expectation that CO_2 in association with OHP would elicit the same response as CO_2 acidosis at atmospheric pressure—an argument used in the denial of the importance of CO_2 in OHP—appears to be unwarranted. Where, as has frequently been the case in experiments purporting to show the effects of OHP alone, there is any appreciable concentration of CO_2 in the respired OHP, it markedly augments the effects of OHP chiefly by throwing additional load on an already disrupted CO_2 transport system. The presence of severe and extensive pulmonary damage which is sometimes induced by OHP in the more prolonged exposures must also contribute to an increased tissue CO_2 tension and an enhancement of the reactions. Taken as a whole the evidence would appear to fully justify the conclusion that the increased CO_2 tension constitutes an important etiological factor in poisoning by OHP. On the other hand CO_2 and its disturbed transport by the blood cannot be elected as the only etiological factor.

4. *Increased Tissue Acidity as an Etiological Factor.* An increase in CO_2 tension in the tissues implies an increase in tissue acidity and, barring some peculiar specific action of CO_2, it is fair to assume that the action of CO_2 in OHP is attributable to its acid properties. Stadie, Riggs and Haugaard (1944) point out that as a result of failure in the reduction of oxyhemoglobin in OHP one should expect an increased acidity of venous blood. That an increased blood acidity does occur under these conditions was demonstrated in experiments mentioned above (Bean, 1929, 1931). This increase may be safely accepted as reflecting a shift of tissue pH to the acid direction. The findings of Campbell (1929) also indicate the tissue acidity increased in exposures to OHP. Bert (1878) speculatively remarked that tissue acidity might be increased in poisoning by OHP and be the cause of death.

Behnke, Shaw, Shilling, Thomson and Messer (1934), while granting that an increase in acidity of venous blood is possible (they found by indirect methods, a change in pH from 7.33 to 7.30) when oxyhemoglobin is not reduced, concluded that this increase is so small as to be insignificant as an etiological factor in O_2 poisoning. Behnke, Johnson, Poppen and Motley (1935) on the basis of experimental data from human subjects state that "Increased tissue acidity resulting from exposure to oxygen is ruled out by the constancy of the respiratory minute volume at 1, 2, 3 and 4 atmospheres' pressure. While there are minor fluctuations in minute volume, there is no consistent tendency toward an increase as the oxygen pressure is raised."

Other things remaining constant, an increase in ventilation at atmospheric pressure does suggest increased tissue acidity; on the other hand it would seem unwise to assume that respiratory minute volume by itself constitutes an infallible index of the degree of tissue acidity, particularly in exposures to OHP. Certainly hyperpnea and dyspnea are common characteristics of the response of anesthetized (urethane) animals to OHP, yet prolonged apneas have occasionally been recorded in such exposures (Bean, 1932).

The lack of an exact parallelism between the degree of hyperpnea and the

acidity of the tissues in OHP is indicated by the finding (Bean, 1931) that the greatest increase in blood acidity very commonly occurred in those animals whose breathing was least increased by the OHP. This emphasizes the importance of the hyperpnea in OHP as a compensatory reaction against an increasing tissue and blood acidity.

The fact that increased CO_2 does not under all circumstances or in all concentrations result in increased breathing attests to the inadvisability of assuming that an increased CO_2 tension and the consequent increase in tissue acidity invariably elicits hyperpnea. Marshall and Rosenfeld (1936) and Moyer and Beecher (1941, 1942 a, b) found that the administration of O_2 at atmospheric pressure to anesthetized (barbiturates) animals subjected to increased CO_2 tensions, resulted in diminished breathing and even apnea. These findings provide evidence of both the fallacy and the danger of assuming that increased CO_2 tension and the accompanying elevation of tissue acidity always increases breathing. The decreased breathing and occasional apnea which not infrequently occur in the late stages of exposures to OHP may be due, in part at least, to a somewhat comparable reaction of the organism to increased CO_2. Similarly, the less pronounced response to OHP, of animals decerebrated under evipal anesthesia (Bean and Rottschafer, 1938) and the relatively low percentage of animals anesthetized with barbiturates which were convulsed by OHP (Behnke et al., 1934), may find partial explanation in this action of increased CO_2 tensions in the tissues.

Bert (1878) reported that the presence of CO_2 in the respiratory medium diminished the occurrence of O_2 convulsions even though the severity of the exposures might be such as to cause death. He attributed this absence of any marked response of some subjects (birds) to OHP, to the CO_2 which acted on the tissues as an anesthetic to prevent the seizures in a manner similar to that of chloroform. It should be emphasized, however, that because under some circumstances increased CO_2 diminishes breathing, it does not necessarily follow that excess CO_2 must have attained such proportions as to depress the underlying vital phenomena; it may very well be that distinctly lesser concentrations of CO_2 might diminish breathing or hold it temporarily in abeyance, not because of a depressant influence but rather simply because of an interference with, or maladjustment of, the normal integrative mechanisms. The respiratory records presented by Behnke et al. (1935) do not include any tracing of the respiratory minute volume obtaining under exposure to OHP but those tracings which are shown of the breathing in O_2 at atmospheric pressure do illustrate distinct respiratory changes. The authors suggest that these changes were caused by an increased sensitivity to CO_2, induced by the increased O_2 tension.

The conclusion of Shaw, Behnke and Messer (1934) agrees that even a relatively slight increase in CO_2 tension becomes peculiarly effective in the presence of OHP and this implies a similarly enhanced significance to the attendant small increase in acidity. Incidentally the results of these experiments illustrate how misleading it is to assume, that because a certain chemical change in an animal appears to be "insignificant" under conditions of normal pressure, it should re-

retain that same insignificance under the vastly different adjustments obtaining in an animal exposed to OHP.

The acceptance of increased acidity as a significant contributor in the reactions to OHP is indicated in the report of Behnke and Willmon (1939) on their investigation of the use of OHP in deep-sea diving. In contrast with the conclusion of Behnke et al. (1934) on the insignificance of a pH change of from 7.33 to 7.30 these authors state that one of the factors "worthy of emphasis" is, "that the acidity of the venous blood is increased by a pH change of 0.03 when oxygen is inhaled." On the whole, then, the experimental findings and interpretations of earlier workers regarding the significance of CO_2 and increased acidity in poisoning by OHP find support and confirmation in the later work of other authors who, having originally denied the importance of these factors, have later come to recognize their potency.

One of the various possible modes by which increased acidity might conceivably contribute to the reactions of poisoning by OHP which deserves mention is the effect which increased pH has on synaptic physiology. Gesell, Brassfield and Hamilton (1941, 1942) have presented evidence that one of the determinants of the intensity and duration of cell activity is the pH at the site where cell activation is normally accomplished by the physiologically liberated acetyl-choline. Increased cH serves to protect this humoral substance from destruction, thus its duration and intensity of action are increased. One might therefore suspect that an increased tissue acidity arising from the various conditions obtaining in OHP would contribute to the general reaction of the organism by virtue of its influence on the longevity of acetyl-choline.

Questioning whether the response of isolated smooth muscle to OHP might not be due to increased concentration of acetyl-choline liberated from intrinsic nerve endings Bean and Bohr (1940) found that atropinization failed to prevent the typical response of the tissue to OHP and inferred therefrom that the effect of OHP on isolated smooth muscle was not due to acetyl-choline. On the other hand the same authors observed (1940, unpublished data) that OHP does not eliminate the action of acetyl-choline artificially administered to tissue under pressure. While these results suggest that the potentiation of acetyl-choline by increased acidity does not play an essential rôle in the O_2 poisoning of isolated tissue preparations, they do not rule out the possibility of its involvement in O_2 poisoning in the intact animal. The problem calls for further experimental work. In this connection the fact that the normal destruction of acetyl-choline is accomplished through the enzyme cholinesterase is of especial interest for if OHP inhibits cholinesterase as it does some other enzymes, acetyl-choline effects should thereby be augmented.

The probability that CO_2 enhances the toxic influence of OHP by virtue of its acid properties, demands a consideration of other mechanisms operative in OHP which may lead to an increased tissue acidity, for example, the decreased metabolism which occurs under such conditions.

5. *Decreased Metabolism as an Etiological Factor.* In considering changes in metabolism, cognizance must be taken of the fact that many reports to the effect

that OHP causes a decrease in metabolism have been based upon data taken from experimental animals in those terminal states where such decrease would be expected as a part of the slowing up of all vital phenomena preceding actual death, and do not, therefore, represent any action peculiar to OHP. However, even after necessarily discounting such data there remains convincing evidence that OHP does have a depressant action on metabolism.

The significance attached to the decrease in metabolism induced by exposures to OHP has been variously interpreted. Campbell (1937a, b) has maintained that the decrease in body temperature of animals exposed to OHP, is a protective metabolic reaction against the toxic influence of OHP. Ozorio de Almeida (1934) believed that the decreased metabolism in OHP is the cause of the pulmonary damage and convulsions induced by OHP. Bert held that it represented the actual death of the cells. This decreased metabolism may conceivably represent an ultimate etiological factor in the poisoning by OHP, or it may on the other hand contribute to the reaction by augmenting the tissue acidity. According to Bert the oxidations in animals possessed of hemoglobin failed because the O_2 was not derived from the oxyhemoglobin, the implication being that O_2 so derived had some peculiar property essential to oxidations not possessed by the O_2 which, under OHP comes directly from simple solution in the blood and tissue fluids without intermediary association with hemoglobin. Nevertheless in those forms of life devoid of hemoglobin it was maintained that the excess of dissolved O_2 alone decreased the oxidations. It was further claimed that the decrease in oxidations induced by OHP, unlike that resulting from exposure to low O_2, was caused by some toxic substance which, produced by the OHP, persisted in the body after the animal's return to normal environment and resulted in ultimate death.

There are however several conditions obtaining in animals exposed to OHP which suffice to explain this decreased metabolism without the necessity of resorting to the introduction of a hypothetical toxic substance. Among such conditions are the increased CO_2 tension and tissue acidity, both of which depress tissue oxidations; another is a direct action of OHP itself on the intimate mechanisms of cellular respiration.

6. *Direct Action of Oxygen at High Pressure; Enzyme Involvement.* That OHP has some more direct action on tissues other than that effected through increased CO_2 tension and its disturbed transport by the blood, is demonstrated by the fact that it adversely affects isolated tissue preparations, and kills or injures organisms which possess neither circulatory system nor hemoglobin; and since increased O_2 tension, or pure O_2, even at atmospheric pressure inhibits many types of enzyme activity (see section I) it would appear that one important avenue through which a direct action of OHP might be accomplished, would be an attack upon cellular enzyme mechanisms. The early experiments of Bert provide suggestive evidence that OHP does impair enzyme activity; he pointed out that the more intimate vital phenomena were affected. But his own general conclusions regarding the effects of OHP on ferments, if correct, would appear to rule out the possibility that enzymes were either directly or indirectly affected

by OHP. According to Bert's designation, enzymes as we now define them would be classed with his "false" ferments—non formed ("ferments non figures") soluble products or extracts of cells—and these he claimed, remained unaltered by OHP. It was only the "true" ferments—living microscopic organisms—that were adversely affected, as he says, "les organismes microscopiques qui constituent les vrais ferments . . . sont tués par l'oxygène; qu'au contraire, les ferments non figurés, solubles, les diastases, lui résistent parfaitement et sont même conservés par lui."

Bert observed that although the putrefaction of meat was suspended by its exposure to OHP, it turned acid in reaction; no tests were made but he suggested this might be due to an accumulation of lactic acid as a result of the suspension of the fermentation processes by the OHP. Unaware of these early speculations of Bert, Bean and Haldi (1932) posed the question of whether the decreased metabolism induced in animals by OHP might not be reflected in an alteration in the lactic acid of the blood. Finding a reversible increase in the blood lactic acid of urethanized dogs exposed to OHP these investigators suggested in explanation, that the toxic effects of OHP involved a poisoning of enzymes with a resultant disturbance in oxidative processes.

The experiments of Meyer (1927) provide direct evidence that OHP alters enzyme activity; that author found that suspensions from macerated brain tissue which had previously been exposed to O_2 at pressures slightly less than 4 atmospheres for 4 hours, were less efficient in oxidizing guaiacum in the presence of hydrogen peroxide than those of similar tissue preparations which had been exposed to atmospheric air for an equal period. It was concluded that OHP caused a decrease in metabolism of the brain.

Libbrecht and Massart (1935) found that in the blood of rabbits which had been convulsed by exposures to O_2 at 4 atmospheres for 30 minutes, the ratio of the oxidized to reduced glutathione was decreased to one-tenth of its normal value and believed this was causally related to the impaired oxidation in the tissues which obtains in such exposures. Libbrecht and Massart (1937) using a chamber which provided means of controlling the necessary experimental procedures from outside, studied the effects of OHP on the preparations in question while they were still subjected to the increased pressure. They found that the exposure of fresh succino-dehydrogenase preparations to O_2 at between 4 and 5 atmospheres poisoned the system so that the O_2 consumption was completely stopped. But in experiments in which the activity of the cytochrome system in the preparation had previously been eliminated by the use of cyanide, this poisoning of the dehydrogenase system was absent. The authors concluded from this that molecular O_2 is not toxic but that it becomes so when activated by the cytochrome system; according to them it is active O_2 which inhibits the dehydrogenase system.

Stadie, Riggs and Haugaard (1944) state that the term "l'oxygène actif" of Libbrecht and Massart is not sufficiently specific and suggest that perhaps the hypothesis of these authors might be "re-framed by stating that the cytochrome system together with the oxygen at high pressures oxidizes the succino-dehy-

drogenase to an inactive form." But in their own experiments Stadie and associates found no evidence to support this hypothesis.

Yet the experiments on rabbit intestine (Bean and Bohr, 1940, unpublished data) indicate that the cytochrome, or some other cyanide-sensitive system does play a rôle in the toxic action of O_2 at high pressure on isolated tissue for it was found that although O_2 pressures of from 3 to 6 atmospheres caused a rapid drop in the tonus of isolated pyloric sphincter, this depressant action of high O_2 pressure could be eliminated by previously treating the tissue with NaCN which of itself caused no change in tonus. The fact that NaCN caused no appreciable change in tonus of the pyloric sphincter was interpreted to mean that the maintenance of tonus in that tissue is not dependent upon a cyanide-sensitive system and since in the absence of NaCN, O_2 at high pressure causes a sharp drop of tonus it would appear that O_2 at high pressure affects enzyme systems other than those which are cyanide-sensitive. The results suggested further that the enzyme systems responsible for the maintenance of tonus in the pyloric sphincter and in the circular duodenal muscle are not identical.

Bohr and Bean (1940) in experiments on fresh extracts of pork hearts found that exposure to O_2 at pressures of 7.5 atmospheres, irreversibly decreased succino-dehydrogenase activity by as much as from 9 to 50 per cent, and suggested that the incomplete reversal of the toxic effects of OHP on isolated tissues previously noted, might be explained by such an irreversible inactivation of enzyme function. These authors proposed that considerable variation in the degree of inactivation of the enzyme preparations by OHP might explain the striking individual variation in the susceptibility of animals to the toxic effects of OHP so frequently observed. The greater resistance of young animals to the toxic action of OHP, as reported by some investigators, the enhancement of resistance by thyroidectomy (Campbell, 1937b) and by starvation (Ozorio de Almeida, 1934) might also be explained by a certain enzyme state peculiar to each of those conditions. The great variety of susceptible enzyme systems may further contribute to the wide variation in the susceptibility to the toxic action of OHP seen not only in different individuals but also in different animal forms.

By far the greater part of the evidence of enzyme inactivation by O_2, which at best is limited, has been derived from experiments carried out with increased tensions of O_2, or pure O_2, at atmospheric pressure and it is not unlikely that some of this evidence is applicable also to the effects of O_2 at pressures of several atmospheres. But in assuming that the same effects, somewhat enhanced, should necessarily occur in OHP as in O_2 at atmospheric pressure some caution may be demanded. The case of hemochromogen enzymes may perhaps be illustrative of this. Hoberman and Rittenberg (1943) found that hydrogenase along with hydrogenlyase, enzymes first described by Stephenson and Stickland (1931), is reversibly inactivated by oxygenation for 24 hours. This inactivation was attributed to an oxidation of a heavy metal portion of the enzyme which they believed was an iron porphyrin-protein complex. They concluded that in the presence of O_2 the enzyme is in the oxidized state but in the presence of hydrogen and reducing agents it is in the reduced state. According to this, then,

the toxic action of O_2 on the enzyme, previously noted by several investigators (Stephenson and Stickland, 1931; Wilson, Lee and Wilson, 1942), might be explained simply as the transformation of the iron to the oxidized state, in which form the enzyme is inactive, whereas reduction of the iron constitutes a reactivation of the enzyme and so reverses the toxic action of the O_2.

Stadie and associates (1944) accept this as one of the well substantiated theories of enzyme inactivation by O_2 but their own experiments showed that catalase, which is another hemochromogen comparable to that of hydrogenase, was not inactivated by O_2 even at high pressures. The authors point out that this indicates that all iron or metallo-hemochromogen enzymes may not react in the same way to O_2. However, perhaps one may question whether these results may not also indicate that hemochromogens react differently in O_2 at high pressure than they do in increased O_2 tensions at atmospheric pressure. Hoberman and Rittenberg found that increased pressure of heavy hydrogen in their experiments (470 mm. Hg) decreased the activity as compared with that at a pressure of 30 mm. Hg.

Another reason for questioning the expectation that the effects of O_2 on enzymes at high pressure should be the same as those at atmospheric pressure is the fact that catalytic action in some purely physico-chemical systems has been found to be distinctly altered by increased pressure. One explanation offered for this is that increased pressure induces a molecular rearrangement at interfaces. There would seem to be no justification for denying the possible occurrence of similarly important molecular rearrangements in biological systems.

In spite of the probable differences in the effects of O_2 at atmospheric and at high pressures, the literature concerning enzyme inactivation by O_2 at atmospheric pressure offers a variety of suggestive possibilities by which OHP may inhibit enzyme activity. Stadie and associates (1944) group those they consider most significant as follows: (1) oxidation of a co-enzyme to the inactive oxidized form; (2) oxidizing activating sulfhydryl compound; (3) oxidizing active —SH groups of the enzyme molecule; (4) oxidation of metallo-hemochromogens to inactive oxidized forms; (5) oxidizing the activating metal constituent; (6) formation of an inhibitor from precursor other than the enzyme; (7) alterations in the oxidation-reduction potential of the medium.

Fahr (1941) reported that intra peritoneal injection of lactoflavin, nicotinic acid amid ("Nicobion" Merk) decreased the toxic action of OHP (4 to 6 atm.) in subsequent exposures. Glutathion likewise was of some, but much less, benefit. These effects were thought to be explainable on the basis that OHP had a toxic action on a redox system in the enzyme mechanisms.

The activity of most enzyme systems is sensitive to changes in the reaction of their immediate environment so that even relatively small shifts in pH become very significant. This is illustrated by the pH curves of Wilson, Lee and Wilson (1942) which show that a sharp decrease in the activity of the enzyme hydrogenase occurs (at atmospheric pressure) when the pH falls only slightly below the optimum of about 7.3. The striking enhancement of the reaction to OHP, both in animals possessed of hemoglobin and in those such as Drosophila which

are devoid of this pigment, may find an explanation then in the acid effect of CO_2 in combination with the influence of OHP itself, on tissue acidity. This would appear to be particularly significant since the optimum pH of many enzymes other than hydrogenase are in the neighborhood of 7.4 (Koehler and Reitzel, 1925; Lehmann, 1935; McGowran and Rheinberg, 1933).

In summary then it may be said that the evidence from experiments on isolated tissues, and extracts therefrom, together with data on enzymes from other sources, indicate that fundamental cellular metabolism can be altered by a direct action of OHP on enzymatic processes. This direct action, operative in the absence of a circulatory system, is not dependent upon a disturbed CO_2 transport function of hemoglobin.

The fact that CO_2 augments the toxic effects of OHP on organisms devoid of hemoglobin such as Drosophila and some bacteria must mean that CO_2 has some distinct adverse effect of its own, perhaps due to its acid properties, when associated with OHP or that it potentiates the direct toxic action of the OHP on enzyme systems.

In those animals possessed of hemoglobin the direct effect of OHP on tissue enzymes must share a goodly portion of the responsibility for the reactions and decreased metabolism which exposure to OHP induces. But in these animals there is, in addition to this direct effect of OHP by itself, the increased tissue CO_2 tension and tissue acidity consequent upon a disturbed CO_2 transport. This CO_2 acting in the presence of OHP, perhaps in a manner similar to that suggested above in connection with response of animals devoid of hemoglobin, augments the reactions of the animals to OHP.

If, further, there be CO_2 present in the environmental OHP or if CO_2 elimination at the lungs is impaired, there is thrown an additional load on an already disrupted CO_2 transport system and there results a more rapid onset and a still further augmentation of the intensity of the OHP reaction. The direct toxic action of OHP on respiratory enzymes, the influence of increased CO_2 tension either by itself or in some potentiative combination with OHP on enzyme mechanisms, and the acid effect of CO_2, all tend toward an increased tissue acidity and decreased metabolism. In OHP, the situation would seem to be such that not only does increased acidity, such as that arising from CO_2, disrupt enzyme activity, but also that OHP, by directly disrupting enzyme activity, further increases tissue acidity.

7. *Hyperoxic Anoxia.* The reactions of isolated longitudinal muscle of rabbit duodenum, to OHP, to sodium cyanide, and to low O_2 have been found (Bean and Bohr, 1940) to be so very similar as to suggest that a common factor is operating in all three conditions; this might very well be an increased tissue acidity, which in the case of both the cyanide and the OHP may arise from the diminished O_2 utilization consequent upon a poisoning of respiratory enzymes. Or it might be that the low O_2 utilization, which amounts to a hypo- or an anoxia, is itself the more fundamental factor common to these three conditions. This seemingly paradoxical relationship where, in OHP, the superabundance of O_2 induces tissue changes and elicits responses, which are typical of those induced by O_2 deficiency, has been referred to as "hyperoxic anoxia."

There are numerous other observations, especially those from intact animals which lend support to the view that in both anoxia, and in poisoning by OHP, the same fundamental processes are affected: For example, it may be more than coincidental that the nausea, vomiting, defecation, pupillary dilatation, muscular tremors, prostration and convulsions seen as symptoms of cyanide poisoning, of asphyxia and of the anoxia of altitude or mountain sickness, are also found in poisoning by OHP. Ravenhill (1913) found that convulsive seizures occurred in altitude sickness; Kaunitz (1942) observed anoxemic convulsions in mice; and convulsions occur not infrequently in routine testing of aviation cadets in low pressure chambers (Gemmill, 1942).

Haldane and Priestley (1935) pointed out that in diving operations where the O_2 of the respired gas was about 2 atmospheres, the reactions of the workmen, particularly the loss of memory and abnormal behavior, "were strongly suggestive of an effect on the brain . . . similar to that caused by too low an oxygen-pressure." The several reports to the effect that young animals are more resistant to the toxic action of OHP than older ones constitutes still another point of similarity between O_2 poisoning and anoxia, since it is found that young mice are more resistant to cyanide and to asphyxia than old mice (Reiss and Haurowitz, 1929).

Further suggestive evidence that the toxic action of OHP may be essentially due to an anoxia is found in the similarity between some of the late responses to OHP in experimental animals (disturbed equilibrium, neuro-muscular incoordination, gait and posture) and those of alcoholic intoxication, the effects of which have been long likened to those of low O_2 (Ravenhill, 1913; Barcroft, 1920, 1925; Haldane and Priestley, 1935) and have been more recently recognized as a form of real anoxia (Palthe, 1926; MacFarland and Barach, 1936; MacFarland and Forbes, 1940).

It is well recognized that anoxia may be attended by striking changes in personality and this too has a counterpart in poisoning by OHP; docile, tame white rats have not infrequently been changed to combative vicious, biting animals by exposure to OHP. Another feature common to both low O_2 and to OHP, is the wide individual variation in susceptibility to the deleterious action of each of these conditions. Finally OHP (Ozorio de Almeida, 1934) like low O_2 (Monge, 1942, 1943) causes sterility in male animals.

Taken as a whole the evidence forms a rather substantial basis for the interpretation that hyperoxic anoxia arising from enzyme poisoning, and intimately bound up with tissue acidity, constitutes an exceedingly important etiological factor in the production of, if it is not the ultimate cause of, the toxic action of OHP; an animal poisoned by OHP is in effect then drowned in O_2.

8. *Increased Oxidation in the C.N.S.* Finding that thyroidectomy increased the resistance to the toxic effects of OHP, Campbell concluded (1937b) that O_2 poisoning is due to an "excessive and rapid oxidation in the nerve cells, and that the usual end products of metabolism, e.g., carbon dioxide, are responsible for the poisoning." Bounhiol (1929) likewise held that metabolism was increased by OHP and suggested that this, in conjunction with an impaired removal of metabolites, would result in an excessive accumulation of metabolites which

would eventually slow and limit the reaction in conformity with the law of Le Chaletier.

Certainly in view of the disruption in the carriage of CO_2 by the blood as occurs in OHP, and the peculiarly high potency of CO_2 and OHP in combination on cellular processes, anything which augments metabolism, such as increased thyroid activity or elevated body temperature, should be particularly effective in hastening the onset, and enhancing the severity of the reaction to OHP. To date, however, there appears to be no very reliable indication that OHP does increase metabolism; in fact with few exceptions the evidence, as previously stated, points to the contrary. Campbell (1937a) has himself maintained that the fall in body temperature which, according to a number of investigators takes place in OHP, constitutes a protective reaction against its toxic action. Granting that such a drop in temperature does take place and that it serves a protective function it is difficult to reconcile such effects with the proposed concomitant increase of metabolism within the C.N.S.

It has been generally accepted that an increase in environmental temperature does augment the toxic action of OHP but in spite of the importance of the temperature factor in O_2 poisoning, a fall in body temperature is not necessarily a guarantee against the occurrence of the toxic effects; nor is an elevation in temperature a sure index that convulsions will occur. The temperature of Thompson's alligator rose from 51° to 75°F. during an exposure to O_2 at a pressure of about 4 atmospheres, and under ordinary circumstances it would be fair to assume that there was an accompanying increase in metabolism, yet no convulsive attack occurred. On the other hand his warm-blooded animals, the temperature of which dropped during the exposure, suffered severe O_2 convulsions. These observations argue against the excess oxidation theory of O_2 poisoning. But even if this theory were entirely acceptable, the increased oxidation would only be an intermediate step on the road to a more rapid CO_2 accumulation, to increased tissue acidity, and thus to the eventual disruption of normal oxidative processes.

9. *Toxic Substances.* The idea that poisoning by OHP might be due to some toxic substance seems to have originated with Bert, who, as already mentioned, claimed that the reactions to OHP, particularly the convulsive seizures, must be due to some toxin produced by OHP and which primarily affected the C.N.S. and continued to do so even after the animal's return to normal atmospheric pressure. He was unable, however, to reproduce in normal animals either the convulsions or any of the symptoms of O_2 poisoning by transfusion of blood from those suffering O_2 poisoning. He concluded therefore that the convulsive seizures were not due to circulating toxins. He did hold, nevertheless, that death from OHP was caused by some toxic substance produced in the tissue by OHP as he says, "Il semble qu'il se soit, sous l'influence de l'oxygène comprimé, formé dans les éléments anatomiques qualque produit toxique, qui ne peut pas toujours s'éliminer, et tue alors mème que sa cause formatrice a disparu. Aller plus loin que cette hypothese me paraîtrait une impudence dans l'etat actuel de la science."

The observation of Barsoum and Gaddum (1936) that the blood of patients

suffering from superficial burns from high temperature in the 21 per cent O_2 of the normal atmosphere contained increased amounts of histamine, suggested to Campbell (1937c) that OHP (4 to 6 atmospheres) at 33°C might lead to similar "burning" of some tissue, especially that of the lung, and result in an increase of blood histamine. This view, reminiscent of the early theories regarding the incendiary action of O_2 on the lungs was tested experimentally. It was found that blood histamine of rats exposed to O_2 at 5 atmospheres was about 3 times that of normal rats; yet histamine injected into normal rats failed to produce the symptoms of O_2 poisoning or to augment the symptoms induced by exposure to OHP. Attempts (Campbell, 1937b) were made also to duplicate the picture of O_2 poisoning by injecting into normal rats not only the blood but also extracts of brain and liver from rats previously poisoned by OHP. These injections likewise failed to elicit the response of O_2 poisoning; injections of similar extracts mixed with thyroxin were also without effect. The experimental results of Iwanow, Krawtschinsky, Prikladowizky and Ssonin (1934) likewise failed to prove O_2 poisoning was caused by some special toxic substance, and Bean and Bohr (1940) were unable to demonstrate that any toxic substance was released from isolated smooth muscle poisoned by OHP.

10. *Psychological Factors.* In connection with the discussion of the effects of compressed air some stress was laid on the fact that man or other experimental animal under emotional strain is not quite the same chemical or physical machine that he is under ordinary circumstances. This would seem to be applicable also in the exposures to OHP; while a given chemical or neuromuscular adjustment of psychological origin might exist at atmospheric pressure without gross manifestations, the superimposition of OHP may provide a combination which induces reactions which would not be precipitated by each of these conditions alone. The evaluation of such combination of conditions is extremely difficult, if not impossible, but such difficulty provides no excuse for their dismissal as non existent.

In experiments on rats known to be particularly susceptible to audiogenic convulsions, the reviewer has observed that the noise of the escaping gas, as occurs on decompression from increased pressures, has in several animals been sufficient to precipitate seizures. It is not unlikely therefore that the addition of the audiogenic influence to that of the convulsant action of OHP may, in some instances, help to precipitate reactions to OHP which otherwise might not occur. This suggests the possible importance of an involvement of psychological factors in the precipitation of both the subjective and the objective reactions to OHP. The wide individual variation in the psychological element may provide another explanation for the wide individual variation in the response to OHP which has been so commonly observed in both man and other experimental animals.

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* In a report which appeared after the type for this review had been set up, Reinhard et al (1944) described effects of O_2 at from 70 to 100 per cent concentration administered at atmospheric pressure by mask over several periods of from 8 to 20 days duration to 4 human sickle cell anemia patients. They found a decrease in the degree of intravascular sickling of red blood cells, no consistent change in the rate of hemolysis, a depression of erythrocytogenesis and a post-administrative increase of circulating leucocytes. The toxic manifestations of the O_2 administration were considered as of only minor significance; their case reports include the following; sore throat and fever, pains of from mild to severe intensity in the legs and back during and after the O_2 administration, numbness tingling and stiffness of the hands and feet, sharpshooting pains in the chest, intense headaches persisting for a week after the cessation of the O_2 therapy, feeling of exhaustion and profound weakness, anorexia and loss of weight, nausea and prolonged vomiting, peculiar taste sensations, impairment of hearing, dizziness, muscle soreness, cough with mucoid sputum, hoarseness, burning sensation in nose and throat, epistaxis, swelling and oedema of mucous membranes. (Reinhard, E. H., C. V. Moore, R. Dubach and L. Wade. J. Clin. Invest. **23:** 682, 1944.)