

Oxygen Toxicity and Anesthesia: A Ten-Year Review and Overview*

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The awareness of anesthesia personnel in the entity of "oxygen toxicity" has been increased in the last ten years by the greater involvement in prolonged respiratory care, and concomitantly increased complexity of operative management. The realization that cyanotic heart disease and primary pulmonary insufficiency does not necessarily protect the individual against the occurrence of the pulmonary manifestations of the disease, and that further *realistic* delineation of the parameters of control is necessary, has focused an intense beam of critical reevaluation on present methods of anesthetic management and postoperative care. It is important to note that "oxygen toxicity" as commonly discussed, that is, the CNS, pulmonary, and eye manifestations, represents advanced stages of the body's adverse responses. More frequent and subtle changes are present, but often overlooked. This is particularly true in the less easily discernible effects upon electron transport systems, and interference with basic membrane and enzymatic function.

As individuals trained in the management of cardio-respiratory emergencies, anesthesia personnel may expect to be called upon professionally regarding problems related to the management of dysbarism and oxygen toxicity; particularly in view of the currently developing underwater industrial and agricultural interests producing greater numbers of exposed individuals and radically different environmental conditions complicating acute medical care. The feasibility of returning individuals to the surface is poor. This would necessitate prolonged periods of decompression and would introduce serious problems of logistics.

A good deal more emphasis should be placed

on the continuing study of oxygen effects by anesthesia laboratories and the possible interaction of the gas with other drugs as related to liver and kidney function, enzyme activity, membrane function, and electron transport. The information obtained will have broad ramifications in our total understanding of uptake and distribution, rate, and excretion of the anesthetic agents currently utilized, and hopefully will lead the way to the introduction of less noxious and more easily controlled agents and a more careful and logical physiological approach to patient management.

Historical Review. The concept of "oxygen toxicity" is anything but new, dating back to the time of Lavoisier, and followed in 1849 by Smith's description of a fatal pulmonary "inflammation" after exposure to oxygen at 3-5 atm for approximately 24 hours.

Insofar as the impact on anesthesia is concerned, in the last 15 years, during which time the problems began to affect the care of patients, the primary consideration was the pulmonary manifestations of the "disease." Perhaps, "iatrogenically induced disease" would be a more appropriate expression. This concentration on the pulmonary manifestations was natural in a nonhyperbaric environment, particularly since anesthesiologists had been more intimately involved with sufficient oxygenation of the patient during surgery, and the maintenance of a proper airway.

Although equally concerned about acid-base balance, carbon dioxide retention, prevention of atelectasis, and a reasonably reactive and physiologically intact postoperative patient, it was not until four major alterations occurred in patterns of patient care that the dynamic characteristics of oxygen toxicity and its relationship to this particular specialty became more obvious. These changes were: (1) The advent of open heart surgery, using the pump-oxy-

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generator, with the special problems resulting therefrom, (hemolysis, air embolism, and marked acidosis). (2) The use of hyperbaric facilities for the surgical and medical treatment of patients with surgical, medical, infectious, and cardiovascular diseases, and their attendant acute threat of oxygen toxicity; that is, *central nervous system* oxygen toxicity (as well as pulmonary toxicity). (3) The progressive involvement in prolonged postoperative ventilatory care, using continuously assisted and/or controlled respiration by ventilators equipped with only limited controls governing inspired oxygen tensions; and the nonconcomitant realization that such care was inducing or producing toxic pulmonary and/or other manifestations, or at least it was increasing the risk of such problems. (4) The current interest in "halothane hepatitis," enzymatic activation and inactivation, and the basic metabolic consequences produced by anesthetic agents. Some of the biophysical-electro-chemical-enzymatic and substrate actions may indeed be similar, as will be discussed further. The fascinating, multifaceted, and increasingly *complex* interwoven nature of the *spectrum* of oxygen toxicity is now only barely appreciated. It seems obvious, and reasonable, that the answers lie in the most basic biochemical processes. The comments in this paper will be oriented primarily toward the clinical aspects of oxygen toxicity as it relates to the practice of anesthesia.

To continue historically, in 1927 the observation was made that cold-blooded animals were much less susceptible to the toxic effects of oxygen unless they were warmed to 37.5°C. At that temperature, even turtles developed fulminating pulmonary manifestations after exposure.

It is known that increased oxygen tension produces changes in the transmembrane potential of frog skin, as contrasted to frog sciatic nerve, and that these changes are irreversible (Gottlieb and Cymerman, 1970). These investigators postulate that the membrane changes are produced by advanced oxidation of the SH groups; that membrane lipids and lipid complexes may have been altered; and that ATP synthesis was inactivated. In a monumentally informative experiment carried out by Chapin and Hohl, one lung of a dog was inflated with 100% oxygen for seven days. The other lung was inflated with air. Only the lung inflated with oxygen showed the characteristic pulmonary changes of oxygen toxicity which shall be described in more detail below.

Dr. Phillip C. Pratt, a pathologist, now at Duke

University and previously associated with the Ohio Tuberculosis Hospital in Columbus, was one of the first clinicians to fully appreciate the early onset and progressive course of pulmonary changes in patients exposed to relatively "innocuous" amounts of oxygen for a period of time. In 1958, he pointed out the similarity of morphological findings in a series of patients, some of whom had received oxygen, for as little as two and one-half days, administered via nasal catheter—not ventilators. He demonstrated capillary congestion and proliferation, followed by the appearance of diffuse fibrosis after a period of about two weeks. Other changes previously noted in experimentally induced pulmonary manifestations were hyperemia, hemorrhage, edema, atelectasis, and "inflammation." These changes had to be differentiated from atelectasis, intrapulmonary hemorrhage, infection, and postmortem alterations due to absorption of gas. A brief experiment followed wherein mice were exposed to 100% oxygen for 48 hours at approximately 740 mm Hg, controlling humidity and temperature. Some of these mice were sacrificed, then autopsied immediately while still in oxygen; others were autopsied after 3 hours in oxygen. There was a significant difference in the appearance of the lungs at postmortem. Air control groups were also used. The lungs of the mice exposed to oxygen, killed in oxygen, and delayed 3 hours before postmortem were hemorrhagic and liver-like in consistency and did not float, thus simulating the characteristic, classical changes of advanced oxygen toxicity, usually thought to occur after more prolonged exposures. Pratt presented the above information at the hyperbaric conference in New York in 1964, and it is particularly noteworthy that he made the following very pertinent comment: "Since this occurs in hospitalized patients receiving oxygen by standard methods such as oxygen tents and nasal catheters, it is apparent that the pulmonary response can result from exposure to atmospheres containing well below 100% oxygen and probably in the range of only 50% oxygen." Pratt went on to discuss the relevant points in making the morphological differentiation between capillary proliferation and the opening of previously "unrecognized" capillaries. (Author's note: "Unused" capillaries. High-oxygen tensions seem to *decrease* the size and number of capillaries utilized, at least in myocardial perfusion and in the brain, as will be discussed later). Pratt felt that vasodilation leading to capillary proliferation was the probable chain of events; that continuous exposure for 24 hours at a

time was necessary; and that intermittent exposures were not cumulative in nature.

In 1964, Heppleston and Simnett found that tissue cultures of pulmonary alveolar epithelium were especially sensitive to oxygen under one atmosphere and equated this exposure to air at 5 atmospheres. They surmised oxygen acts through enzyme inhibition and preferentially affects enzymes possessing SH groups (NS: the statement made previously regarding the transmembrane potentials in frog skins).

Pontoppidan and others have demonstrated similar changes, including the postmortem appearance of hyaline membranes, in patients following ventilation with high-oxygen concentrations. A great deal of emphasis in the last three or four years has been placed on this possible causal factor of patient morbidity and mortality. In 1970, this hypothesis was accentuated by Hamilton and Singer in a study of post-operative cardiac surgery patients. It was their conclusion that fear of "toxicity" should not preclude the administration of oxygen in those patients who needed it. A general opinion still seems to prevail at this time that cyanotic heart disease, and other conditions leading to ventilation-perfusion inequalities, shunting, venous admixtures, and subsequent low-oxygen tensions (and/or hemoglobin saturation), have a protective effect for the patient, and that high-inspired oxygen tensions can be used with considerably less concern. This conclusion is not necessarily valid, as shown by a case report from the Massachusetts General Hospital (New England Journal, May 1970), where it was disclosed that a patient died from pulmonary insufficiency with demonstrated fibrosis following prolonged artificial ventilation. Furthermore, a very important study by Hills indicates that the creation of an artificial shunt producing cyanosis does not necessarily protect an animal from pulmonary injury secondary to high-oxygen tension.

It appears that certain conditions can deprive the individual of protective mechanisms. Artificially altered physiology can produce changes in the reaction of molecular oxygen with SH groups and other enzyme substrates. This effect in turn upsets electron transfer balance and results in additional effects in certain types of cells and subsequently in certain organ systems or "target areas." These effects occur following the administration of such compounds as dipyriddylium dichloride (Clements, Fisher, and Kenneth, 1970); or result from the interaction of other compounds producing changes in certain trace metals and inorganic phosphorous. Mn^{++} and Zn^{++} may have

some effect in preventing the occurrence of lung edema. Mg^{++} seems to have a protective effect against seizures resulting from high-oxygen pressures OHP (Radomski and Wood, 1970). Manganese may act by inhibition of mitochondrial swelling and lipid peroxide formation in the mitochondria; that is, an antioxidant effect. However, similar reactions may also occur producing an opposite effect; that is, sensitization of cells (see below).

The cumulative end results as far as the lung is concerned are: the changes in epithelial cell population; the accumulation of both interstitial and alveolar fluid; and/or proteinaceous material; the deposition of hyaline membrane material; and changes in "surfactant" and its properties. Diffusion is altered, an "alveolar-capillary block" situation develops, shunting occurs, and the patient then has a need for higher-inspired oxygen tensions to achieve any satisfactory saturation, while the "cure" is worsening the disease process!

The warning seems fairly obvious: A minimum oxygen concentration (inspired oxygen tension) should be used to produce an arterial tension of approximately 100 mm Hg and/or a normal hemoglobin saturation depending upon the individual.

Individual variations are very important and should be taken into consideration. These factors include: age, sex, temperature, acid-base balance, type and amount of hemoglobin, MHCH, diet, vitamin levels, and the administration of other drugs. Aspirin and ascorbic acid seem to augment toxicity (Serrill, *et al.*, 1971). Tocopherol deficient animals appear less sensitive to lipid peroxidation in the lung until ascorbic acid and ferrous ions are added (Raskin, *et al.*, 1971). Other factors such as smoking and resultant carbon monoxide levels (Rodkey, *et al.*, 1971) affect the response of the lung. Simple immersion to the head greatly intensifies the pulmonary reaction, primarily by promoting the formation of atelectasis (Balldin, *et al.*, 1971). Stress and its effects, especially increased adrenal output, all adversely affect the individual, as does increased thyroxin.

Conversely, thyroid blockers seem to have a protective effect, as does the administration of sulfhydryl group donors. Others compounds such as ANTU (alpha naphthylthiourea) may act by both actions; that is, by affecting thyroid hormone release, and by providing cellular sulfhydryl enzymes and cofactors in active reduced states (Mountain, 1963). If one can logically accept the argument that there

are individuals who are hypersusceptible to certain noxious or toxic stimuli or compounds, such as those individuals whose susceptible target areas are the red blood cells, which subsequently undergo hemolysis by the interaction with other drugs, then it is just as likely that certain individuals are "pneumonically sensitive." These individuals may react adversely to similar circumstances with the lung as the "target organ."

Opposite circumstances may apply. Certain individuals are hyposensitive. They may react with *increased* resistance, or *decreased* susceptibility, to the action of what are usually considered to be "toxic" concentrations of oxygen. This concept would certainly account for variations from the "usual response," such as the one reported by Kydd: Mice exposed to 550 mm Hg oxygen for 30 days showed only a few of the classical pulmonary changes, but did develop changes in the blood vessels.

Some individuals are susceptible to the occurrence of atelectasis presumably due to absorption of gas (oxygen), plus other factors yet to be determined (Burger, 1967).

A good deal of work has been devoted to the effect of oxygen on succinic dehydrogenase activity in the lung. Until recently it was thought that this was the most important enzyme system affected. However, Bardell and Fowler concluded that other dehydrogenases in lung tissue seem to be more adversely affected. At any rate, return of activity is slow compared to exposure times; that is, 6 hours of exposure to oxygen produced inhibition of the enzymes which returned to normal only after 12 to 48 hours. Interestingly enough in one study pentobarbital seemed to have a protective effect. This conclusion is in contradistinction to the usual *non-protective* effects of anesthetics against damage to the CNS (see below): Residual effects may occur even though convulsions are masked.

Viral and bacterial diseases may grossly alter the individual's sensitivity to toxic agents such as oxygen, and may produce changes in "target areas." (Mountain, 1963). Smoking has a marked additive effect for atelectasis to occur following oxygen exposure. One study indicates that smokers had an in-flight vital capacity loss three times that of nonsmokers (Browning, 1970). Adrenalectomy, chlorpromazine, and sympathetic-blocking agents may have a protective effect, as does hypothermia (Burrows and Edwards, 1970).

There seems to be a cross-tolerance between

some compounds which are considered to be toxic themselves, such as Ozone and NO₂ (Mountain, 1963). Ozone is quite toxic and produces striking epithelial changes including hyperchromatism, hyperplasia, and inflammatory changes. Central nervous system effects also result. Some changes may occur after only a few hours of exposure (Suskind, *et al.*, 1970).

A number of interesting concepts have developed in regard to the pulmonary changes and the manifestations related to oxygen toxicity. A great deal of weight has been given to changes in "surfactant." Earlier, in 1962, the emphasis was on surfactant changes, modification, depletion, and interference with its formation. However, with increasing knowledge in the field, and increasing reliability of investigative techniques, it is beginning to appear that surfactant (changes) may very well be another "target," or, if not a "target," a "system," directly and indirectly involved; resulting from more basic biochemical alterations such as those mentioned above.

"Nitrogen osmosis" is a term referring to an effect produced by the "inert gas" nitrogen, wherein it can pull water away from other solutions of inert gases through certain types of membranes. This is now a popular concept in hyperbaric gas physiology. Such biophysical alteration may very well have some bearing on the mechanism of oxygen toxicity, and the narcotic action of certain "inert anesthetic gases" (neon, argon, etc.). During increased-inspired oxygen tension (thus increased arterial oxygen tensions [pO₂]) a gradient develops between the arterial tension of pO₂ and tissues. This has been called a "steady-state gradient." If certain physical circumstances are prevailing, the movement of water molecules may occur (Hills, 1971). Niinikoski and coworkers are under the impression that the primary effect of oxygen is on the capillary endothelium, producing an increased capillary permeability and a *secondary* "washout" causing a depletion of surfactant and other phospholipids not heretofore considered to be part of normal "surfactants." The mere presence or increase of lipids in such a "washout" does not therefore connote adequate surfactant activity. It may indicate only a "washout," and a depletion of alveolar surface tension reducing materials. Furthermore, one need not find peroxides of lipids, yet detrimental effects of high oxygen may have altered the structural lipids of cells by peroxidation and oxidation and produced subsequent changes in

cellular membranes. These in turn may lead to the release of proteolytic enzymes and even connective tissue elements may be released into the alveoli.

So finally having reached a discussion of "surfactant" after all of the above, it is with the realization that every aspect of "oxygen toxicity" is tied up with the mechanisms and biochemical utilization of the transport of oxygen.

Let us quickly consider the various aspects of alveolar-capillary diffusion pertinent to this discussion (Rankin, 1969). Diffusion can be defined as the movement of molecules of gas from an area of high concentration to an area of lower concentration. As mentioned above, there is direct bearing in relationship to arterial gas tensions. The movements of gases across the alveolar-capillary membrane is determined by: (1) the mean difference in partial pressures of gas on either side of the membrane; (2) the surface area of the membrane; and (3) the permeability of the gas through the membrane. The third is inversely related to the thickness of the membrane. It should be noted at the outset that the total distance for perfusion through the normal alveolar-capillary membrane and the surface lining layer, etc., is of very small magnitude in the normal lung; that is, in the order much less than one micron. The pulmonary diffusing capacity of any gas is determined by the ratio of the quantity of gas transferred per unit time over the mean differences in partial pressure, and is directly proportional to the solubility of the gas and inversely proportional to the square root of the molecular weight (density) of the gas. It is not easy to calculate either the alveolar oxygen tension or the pulmonary capillary tensions. Oxygen tension differences between the alveolar gas and arterial, end-capillary blood are due to incomplete equilibration between the gas and arterial, end-capillaries, and due to the effect of venous admixtures from areas of poor ventilation to perfusion ratios. It should be remembered that pulmonary diffusing capacity must be reduced by $\frac{2}{3}$ before normal arterial oxygen saturation will be affected. This fact should be kept in mind in considering the so called "latent periods" involved in oxygen toxicity in regard to the lung as well as other organs. Diffusing capacity varies with whole body size, metabolic rate, age, levels of lung inflation, alveolar ventilation, intrathoracic pressure, body position, and distribution of inspired gas. The Hamman-Rich syndrome is a classical example of the unfortunate patient who requires increasing amounts of oxygen to his own detriment. There ap-

pears to be excellent correlation between problems in diffusing capacity and pulmonary membrane damage, (etc.). Do the increases in areas of poor \dot{V}/Q which account for much of the loss or decrease in diffusing capacity result from changes in surfactant alone with increased surface tension, or does there occur an increase in pulmonary vascular resistance secondary to the capillary proliferation and "granulation tissue" formation noted by Pratt as one of the toxic effects of oxygen (not the classical effects of hypoxia)? Capillary congestion, an earlier manifestation, may mask problems of diffusion since it will tend to balance them out.

What then is "surfactant," and how does it apply to the concept of oxygen toxicity as we know it in the lung? Many workers have been involved in the field for a number of years: these include Pattle, Clements and Fisher, Morgan, Sutnick, Said, Scarpelli, Tooley, and others mentioned above. A brief summary of their observations and conclusions as it applies to the topic under discussion is now in order.

Surfactant. It would be more appropriate to use the terminology "surfactant systems," "surfactants," or "alveolar lining materials." Unfortunately, until recently at least, the approach has been mostly an anatomical one, utilizing electron microscopy. The electron microscope has enabled investigators to find various structures not heretofore known and has led to certain hypotheses about the origin, function, and elimination of these lining materials. At the outset, it is very important to realize that the lung is not a passive organ responding to filling and emptying, but is a very active one in the body. With a surface area of approximately 70 meters square, and an estimated 300,000,000 alveoli, this fact is quite significant (Scarpelli, 1970).

In 1929, Von Neergaard noticed the differences between fluid-filled and air-filled lungs in the forces needed to ventilate, and pressure-volume relationships. Pattle, in 1955, noted the characteristics of pulmonary edema foam were such as to indicate lowered surface tension. This was followed by the work of Clements and others which showed that a surface-tension-lowering substance was present in lung tissue. Since then, biochemical analysis has indicated that the material is made up of a complex mixture of lipids, protein, and carbohydrates, chief among which is dipalmitoyl phosphatidyl choline (DPL) (palmitic acid). DPL makes up about 50% of the lipid fraction of the layer. This named lipid has been used interchangeably with "lecithin." It is

important to note that the surface-tension-lowering properties depend upon the presence of two *saturated* fatty acid residues. Included in the complex are albumin and carbohydrates (polysaccharides). In the lung, or alveoli as the case may be, a surface interface exists between air and a liquid or hypophase, lining the alveoli. The surface tension along the alveolar lining results primarily from molecular cohesive forces which produce a tendency toward collapse. This force is related to LaPlace's theorem which in turn relates surface tension (T) inversely to the radii of spheres and proportionately to the pressure of gas within the spheres or, as in this case, the alveoli, ($P = 2T/R$). The result is a tendency for liquid to form increasingly smaller spheres, leading to an ever-increasing tendency for collapse. This force is counteracted by the effects of the "surfactant groups," so that a new *end-surface-tension*, in actuality a surface pressure, results. This *surface pressure* force opposes the forces of plasma and other tissue fluids which have a surface tension of about 50 dynes per cm. Considerable elastic recoil results for the lungs. Fortunately, the tendency of the larger alveoli to become larger and larger as the smaller alveoli empty into them (following the above physical laws) is offset. Theoretically, at least, there is some uniformity to alveolar configuration and size, although there is now some doubt as to whether or not alveoli actually exist as true spheres. Maximum intra-alveolar pressures probably exist at the precise moment when the developing hemisphere at the end of the respiratory bronchiole has a diameter equal to that of the terminal respiratory bronchiole. Following this point, some instability and decrease in pressure occurs, with limits of expansion set by the elastic tissue of the lung, and so forth.

Surfactants are considered to be bipolar in nature and to assume this configuration anatomically in the hypophase boundary area. The choline, or *hydrophilic*, group is assumed to associate with the protein area of the hypophase: and the two hydrophobic fatty acid side chains become oriented toward the alveolar air side, forming a compressible film or surface-tension-lowering film. Increased compression, such as would result from collapse of alveoli, actually produces a decrease in surface tension. The result is an equilibration of tensions between the larger and smaller alveoli. The choline group, stated to be associated with protein, contains an ionized quarternary ammonium group which is stabilized by the presence of both calcium and sodium ions.

To summarize briefly: The activity and structure of surfactants is affected by a number of factors, including: (1) heat, which will reversibly inactivate it; (2) changes in pH; (3) the presence of blood; (4) electrolyte concentrations.

It is generally thought that surfactants are produced by "type II" alveolar cells and are secreted into the alveoli where they become incorporated into the lining layer. These are presumed by some to be found as cytoplasmic inclusion bodies, or osmiophilic lamellar inclusions. The inclusions are found in much lower numbers in those species (non-mammalian) lacking or having decreased surfactant levels. Two main theories exist: (1) that the giant alveolar cells form and secrete these organelles or inclusion bodies; or (2) that the opposite is true, the giant cells are responsible for the phagocytosis and breakdown of the surfactants, production being elsewhere—the nonciliated bronchiolar cell for example.

Nonetheless, synthesis turnover is rapid, C14 labeled phospholipids appear in pulmonary phospholipids within 5 minutes after intravenous injection, and a half-life of 14 hours is estimated for the surface active lecithins. It is possible that the entire lipid synthesis of lecithin occurs within the lung itself. The mechanisms of lecithin synthesis can take several paths, as has been nicely described by Morgan. Of import, in regard to the possible effect of oxygen on the system, is the rapidity of metabolism, equating the lung to the liver in some respects. This could produce a result so that any occurrence, physical or chemical, interfering with metabolic generation of either the lipids and/or carbohydrate and protein moieties might throw a natural "monkey wrench" into the system, thus accounting for the so-called "*latent period*" said to exist in the development of oxygen toxicity. The term "latent period" has very little compatibility with basic toxicological hypotheses. The presence of packets of surfactant might slow down the depletion rates and subsequent alterations in activity until such lack of activity produced a fairly rapid onset of symptoms and signs. There is no doubt that the situation is complex. Even the simple concept of a single layer of surfactant is under scrutiny and revision at this time.

Thus indirectly, oxygen may affect organ systems such as the lung through direct action at a very basic metabolic level. Surfactant changes are related to other clinical conditions such as the Respiratory Distress Syndrome of the newborn, changes following pulmonary arterial occlusion with

decrease in surfactant activity; and an excess of surfactant has been postulated in the disease of pulmonary alveolar proteinosis. One must bear in mind that multi-causal factors operate in these diseases, and that the inappropriate administration of "higher than needed" concentrations of oxygen (a somewhat ambiguous phrase) may contribute to the problems developing in various organs through the mechanisms discussed above.

Toxic Effects on Other Systems. Although the primary toxic effects of oxygen at less than one atmosphere (760 mm Hg) seem to be primarily manifested by changes in the lungs, or at least appear to be so orientated from the standpoint of anesthesiology, it is rather illogical to assume that all systems and organs in the body are *not* involved. The appearance of signs and symptoms is related to a time-dose factor, that is, related to exposure and/or circulation.

Two fundamental factors pertain regarding oxygen toxicity: (1) The metabolic consequences occur at the most basic levels of cellular and mitochondrial or membrane activity, and, consequently, must involve all areas of physiology and biochemistry within the body. (2) The "latency" of reaction should more appropriately be called the "time" of reaction. These considerations are certainly more in keeping with the basic toxicological principles of time-dose response. The intensity, duration, susceptibility of the subject, type of exposure, temperature, thyroid activity, presence or absence of other drugs, elements, and trace metals, the condition of the acid-base status, carbon dioxide elimination, 2-3 DPG levels, hemoglobin levels and types, sex, interaction and state of the adrenal-pituitary system and the sympathetic nervous system, perfusion, and other factors all determine which organ system will be affected and at what time.

Central Nervous System Toxicity. The toxic effect of oxygen at higher than ambient (760mm) pressures on the CNS ordinarily does not concern anesthesiologists unless they are operating under specific conditions of OHP in special chambers. However, the entrance of industry, agriculture, and other interests into underwater living and working conditions will produce a much larger population of individuals exposed to dysbarism and oxygen toxicity. It is logical to assume that medical personnel specially trained in cardio-pulmonary resuscitation, and so forth, will be called upon to assist in the diagnosis and therapy of such in-

dividuals. Furthermore, considering the basic nature of the processes of oxygen toxicity, one must have some reservations about the possible adverse effects of oxygen on the CNS at 760 mm or less, other than the well-known vasoconstrictive effects upon cerebral vasculature, and the tendency for hyperventilation which is commonly seen.

Classically, the CNS expression appears as a convulsion, usually beginning with more focal signs such as twitching about the mouth and eyes, and perhaps the small muscles of the hand. It is important to remember that mentation may be quite clear until the abrupt onset of the convulsion, which proceeds through usual tonic-clonic stages. Attempts at *decompression* during periods of glottic spasm may result in rupture of the lungs. Unlike the usual seizure, blood arterial oxygen tends to remain at normal or higher than usual levels if the patient is under OHP (oxygen-high pressure). Central nervous system toxic reactions are intimately involved with pCO₂ levels and acid-base balance, including lactate/pyruvate levels and ratios. Factors other than metabolic ones also pertain, such as circadian rhythms, which may alter the susceptibility to convulsions (Hof, *et al.*, 1971). At three atmospheres (OHP), animals treated with acetylsalicylic acid and/or ascorbic acid, and tocopherol deficient animals, began seizures earlier and died sooner than others (Serrill, *et al.*, 1971). The protective effect of magnesium has already been mentioned.

Anesthetic agents may mask the convulsions of oxygen toxicity, but do not appear to prevent the CNS damage produced by it which commonly results in spastic paralysis, and so forth. In fact, a recent and disturbing study by Lassiter has indicated that in the presence of only 5 psi. exposure to oxygen for two weeks (233 mm Hg) greatly reduced levels of acetylated and unacetylated coenzyme A in the brains of the animals. This occurred in the *absence* of overt signs of CNS toxicity. Apparently, nitrogen seems to have a "masking" or "quenching" effect, casting further doubt about its presumed "inertness." Coenzyme inactivation is postulated to result from: (a) direct oxidation of the sulhydryl groups; (b) from a block in synthesis, produced by oxygen itself through formation of oxygen-metal ion complexes; and (c) by the formation of free radicals elsewhere. These changes produce interference with the transfer of two-carbon units, with a subsequent block of glycolysis, and malfunctioning of the tricarboxylic acid cycle.

A recent paper by Kuperman has shown that the administration of oxygen following bilateral cordotomy may produce sleep-induced apnea, or "Ondine's curse," possibly through effects on the aortic-carotid reflex mechanisms. It can be seen from the above that the effect of oxygen on the CNS is quite complex and only now becoming more fully appreciated.

Effect of Oxygen on Red Blood Cells. As previously mentioned, one of the keys to understanding oxygen toxicity is a clear comprehension of the very complex and, up to now, not entirely clear mechanisms of oxygen transport and its relationship to membrane function.

If one acknowledges the fact that hypoxia per se is a marked stimulant to erythropoiesis, one would assume depression of bone marrow function upon exposure to high concentrations of oxygen. This is not necessarily the case, and the effect of high-oxygen tensions on DPG levels is not entirely clear. There are combined effects of increased $p\text{CO}_2$ levels, difficulties in "unsaturating" oxyhemoglobin, and resultant decreased pH levels (Astrup, 1970). Further influences of the pituitary and thyroid must be considered (Rodriguez and Shahidi, 1971).

Ascorbic acid and ASA may sensitize the red blood cells to lysis (Serrill, et al., 1971). Vitamin E deficient animals are markedly sensitive to the rapid destruction of rbc's, which in part is caused by the actual peroxidation of lipids in the rbc membrane. There appears to be a selective effect on older rbc's (Sabine and Leon, 1971). In certain susceptible animals, such lytic activity may occur at less than one atmosphere, manifesting itself by immediate effects on old cells, and delayed effects on the younger cells which demonstrate decreased mean potential life spans. A diet of alpha tocopherol, an antagonist to lipid peroxidation will abolish or prevent this lytic activity. Several areas are involved, including anerobic glycolysis, hexokinase activity, glucose 6-phosphate dehydrogenase activity, acetylcholinesterase activity, and specific gravity. It appears to be a membrane phenomenon. To confuse the issue even more, one study of angina pectoris and oxygen transport has indicated that its occurrence may actually decrease oxygen affinity of the hemoglobin without changes in DPG levels, possibly secondary to "humoral factors" (Shappell, et al., 1970). One thing is certain, the various metabolic activities involved in oxygen transport and membrane function are not always predictable nor finite,

and changes which occur under one set of circumstances may vary considerably under a slightly different set of parameters, adding to the complexity of response and interaction.

Toxic Effects of Oxygen on Liver and Kidney.

With the current interest in "halothane hepatitis," and the renal effects of Penthrane®, more emphasis should be given to the possible toxic effects of other drugs and agents, and their possible interaction. The multiplicity of factors operating have been discussed above. In 1965, Felig reviewed the literature available on oxygen toxicity at that time and, supported by experiments in Wright Patterson Aeromedical Research Laboratories, came to the conclusion that evidence indicated the following: Exposures to only 258 mm Hg of oxygen for one week produced subcellular hepatic and renal alterations, visible on electron microscopy, in the *absence* of pulmonary histopathology. These changes included mitochondrial enlargement, clumping, and degeneration of membranes. Sodium lactate seemed to have a protective effect; lactate metabolism occurs through oxidation and the transfer of electrons to DPN.

Oxygen at tensions higher than one atmosphere increases lipid biosynthesis (Adams and Norton, 1971). On the other hand, oxygen may indirectly affect protein synthesis by altering dietary habits (Leon, et al., 1971). This could be considered a subtle form of oxygen toxicity.

Insofar as the kidney is concerned, important findings relevant to kidney structure and function were reported by Hess and Menzel in 1971. In animals subjected to dietary depletion, particularly Vitamin A, a 35-day exposure to 100% oxygen produced changes in the proximal convoluted tubules, leading to an increase in lipid levels. These changes were presumed secondary to decreased fatty acid metabolism.

Conclusion. The adverse effect of overexposure to oxygen, that is, "oxygen toxicity," involves virtually every organ system in the body, including the lung, eye, kidney, liver, and erythropoietic systems. The effect follows classic toxicological principles, for the most part relating to time and dose of exposure, which in turn altered by the relative proximity of any particular organ to high-oxygen tensions. Obviously, the lung has the greatest exposure directly. The effect on other organ systems is primarily determined by the circulation and oxygen carrying and transport systems (Skinner, 1972; Siekevitz, 1970).

Most of the emphasis in this paper has been

upon the basic effects of high-oxygen tensions on enzymatic membrane and substrate systems, since it appears that altered biochemistry at these levels determines the ultimate manifestations of the toxic response, be it pulmonary, hepatic, ophthalmologic, and so forth.

More definitive criteria for controlling inspired and transported oxygen are needed. Even the presence of cyanotic heart disease with shunting and desaturation, or primary pulmonary failure per se, do not necessarily protect the individual against the deleterious effects of over-oxygenation. Thus a paradoxical situation develops wherein the administration of oxygen as a lifesaving measure eventually may produce fatal consequences.

Anesthesia personnel will become increasingly involved in situations related to such exposures to oxygen at high pressure (OHP) such as will be found in the new fields of industry and agriculture now being developed underwater, sometimes at great depths. It is the responsibility of the specialty to continue basic and clinical research in these areas and to expand clinical teaching to encompass the management of related problems.

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