The Toxicity of Oxygen

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"It is a matter of common clinical experience that the most varied types of disease involve some damage to the lungs in the form of congestion, oedema or inflammation, and that the danger to life is much increased in any case when such complications supervene." So wrote J. Lorrain Smith,‡ who has received credit for the classic description of the pathology of pulmonary oxygen toxicity. As long ago as 1897, the ubiquity and importance of pulmonary dysfunction in the critically ill were recognized. That he was correct in his understanding of the role of pulmonary dysfunction as a critical factor in diverse disease states is amply borne out by the amount of interest aroused in acute respiratory failure during the last decade.2-5 Smith, a pathologist, also recognized that the inherent toxicity of oxygen might limit its clinical applicability.

His report of the toxic effects of oxygen on the lung6 stimulated decades of research,7-10 but the importance of the syndrome was not appreciated by physicians engaged in patient care, even those concerned primarily with pulmonary disease, until the last decade. The current resurgence of interest in oxygen toxicity is not coincidental. From the clinical standpoint, there was little practical importance to be attached to oxygen toxicity until the advent of efficient mechanical ventilators capable of delivering high oxygen concentrations continuously. With the exception of high-pressure environments, oxygen administration had been largely limited to nontoxic levels3 or the resultant toxicity had been unrecognized.11 This discussion concerns the toxic manifestations of oxygen, with emphasis on the pulmonary aspects, since they are most commonly encountered in clinical practice. Data concerning man's tolerance to oxygen, the pathology and pathophysiology of toxicity, and the underlying mechanisms are reviewed. Finally, possibilities for the manipulation of oxygen tolerance are discussed, and an attempt made at clinical correlation.

Man lives in an ecosystem surrounded by countless environmental variables which impose minima and maxima that define a range within which we exist. That there is a minimum concentration of oxygen compatible with life has been clear since shortly after the discovery of the element.12 Precisely what that concentration is has not been determined in man, but very low values have been described. Measurements by West12 at an elevation of 19,000 feet on Makalu revealed calculated alveolar oxygen tensions as low as 44 mm Hg and arterial levels of 24 mm Hg. These clearly are extremes in acclimated individuals, and extrapolations from such values to the normal clinical situation may not be made. Conversely, it is not surprising that a maximum permissible concentration should also exist for this critical ingredient of life; this was evident to early workers in the field, and was unequivocally demonstrated14 nearly three quarters of a century ago.

There is abundant evidence that the atmospheric concentration of oxygen has not been constant throughout time, and indeed that the fluctuations in oxygen levels may have been a prime determinant in evolutionary history.

Berkner and Marshall15 indicate that life as we know it could not have evolved in the presence of current oxygen levels and that there have probably been two quantum steps in the oxygen history of the earth, one approximately 600,000,000 years ago, at the beginning of the Cambrian era, and another 420,000,000 years ago, at the time of the late Silurian era. These changes occurred simultaneously with the ex-

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Received from the Department of Anesthesiology and the Anesthesia Research Center, University of Washington School of Medicine, Seattle, Washington 98195. Supported in part by USPHS Grants 1 R01 HE14436-01 from the National Heart and Lung Institute, and GM 15891 from the National Institute of General Medical Sciences, National Institutes of Health, Bethesda, Maryland.
THE TOXICITY OF OXYGEN

Fig. 1. The hyperbaric chamber used by Paul Bert in his studies of the toxic effects of oxygen in the 1870s. Cold-water circulation was used to minimize the heat of compression, and the vessel, made of glass, was used at pressures as high as 19,000 mm Hg. Reproduced from *Barometric Pressure* by Paul Bert, edited and translated by Mary and Fred Hitchcock, 1943, with permission of Long's College Book Company.

Explosive proliferation of life forms, in the first case in the sea, and the second on land. They further suggest that oxygen levels have fluctuated since Devonian times in an oscillation around the present "quasipermanent" level. It is clear that oxygen pressures have been far from constant and that they have been both profound determinants of and influenced by the quantity of life on this planet.

Widespread interest in the toxic manifestations of oxygen is rather recent, but some understanding of the phenomenon of oxygen poisoning is as old as our knowledge of the element. Priestley, one of the two discoverers of oxygen, speculated on this possibility in his original communication in 1775. He spoke of oxygen as follows: "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, when the common air would not be sufficient to carry off the phlogistic putrid effluvium fast enough. 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 proper for us in the usual healthy state of 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."

It was not until about 1930 that oxygen was employed therapeutically on a noticeable scale. Technical problems and slow medical progress delayed the common administration of oxygen as a therapeutic agent, and widespread use has come only in the last few decades. Priestley's prophetic statements about oxygen toxicity were to be verified, however, as early as the late nineteenth century. The first account of the observation of oxygen toxicity was, surprisingly, of central nervous system poisoning — surprising because this is a phenomenon restricted exclusively to hyperbaric pressures. Paul Bert, in his monumental treatise, *Barometric Pressure*, published in 1878, dealt extensively with the effects of both high and low pressures, setting the stage for both hyperbaric and altitude research.
Experimenting with birds, he produced convulsions at pressures of 15 to 20 atmospheres of air (fig. 1). Thus, acute central nervous system oxygen toxicity, in the form of grand mal seizures, a manifestation seen only under hyperbaric conditions, was described before any other adverse effect of oxygen. Bert conducted other, more specific, experiments, determining that he could produce the same effect with a fifth the pressure using pure oxygen, and correctly came to the conclusion that the etiology of the seizures was oxygen tension, not barometric pressure or nitrogen. Further, he experimented with oxygen–carbon monoxide mixtures, and demonstrated to his satisfaction that it was the partial pressure rather than the content of oxygen which was critical in determining toxic thresholds. The latter observation remains only partially verified, but it is probably correct.

The other major manifestation of oxygen toxicity in the adult is its effect on the lung. This too, was described in the nineteenth century. In 1899, J. Lorrain Smith described the pulmonary toxicity of oxygen, in an ingenious set of experiments in which he exposed small animals to pressures of oxygen varying between 0.4 and 4.5 atm. Although some of his deductions were confused by the conviction that there was active transport across the lung for oxygen and the belief that the arterial oxygen tension was consistently higher than in air, his descriptions of the observed events are classic. Commenting on exposures of mice to oxygen tensions slightly higher than 100 per cent of an atmosphere, he commented: “The effect on the mice was uniformly fatal, and the immediate cause of death was inflammation of the lungs. Embarrassment of respiration set in some time before death, and the lungs were found post mortem to be extremely congested, with more or less complete consolidation . . . lungs were deeply congested and sank in the fixing fluid. 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. . . . There were no leucocytes in the exudate. The exudate itself was probably the cause of the embarrassed respiration and the animals’ death.” Smith also correctly observed that individual susceptibility to oxygen damage showed great variability, both within and among species.

Human Tolerance to Oxygen

Since Smith’s studies, many others have demonstrated oxygen toxicity in experimental animals. The clinician, however, is concerned primarily with the effects of oxygen in man, and then only within the environmental confines which may be applicable to the clinical situation.

Evidence that occasional patients have survived exposures to oxygen many times greater than was thought possible has led some to question the reality of oxygen toxicity at normal atmospheric pressures as an entity in man. That all mammalian species studied have responded similarly makes it highly unlikely that man is an exception. Despite the difficulty of experimentation in man, sufficient data exist to demonstrate unequivocally that pulmonary oxygen toxicity is a real entity. As long ago as 1939, Becker-Freysang and Clamann found that 65 hours of exposure to 739 mm Hg O₂ produced paresthesias, nausea, and a significant decrease in vital capacity. Since that time, numerous studies of human volunteers breathing oxygen for various periods at partial pressures between 0.7 and 1.0 atmospheres have shown significant changes in vital capacity, minute ventilation, respiratory rate, pH, PₐO₂, total lung volume, carbon monoxide diffusing capacity, and other variables. Many of these studies are difficult to compare, and this creates great confusion in the minds of readers. The oxygen tensions used in the various studies are frequently quite dissimilar. In the older literature, oxygen tensions delivered were frequently not the same as those intended or reported. Durations of exposure vary, as do other factors such as temperature and humidity. In addition to this, there is considerable individual variation in oxygen susceptibility in both man and animals. Despite the plethora of literature available, and the confusion resulting from variations in experimental methodology, there is no doubt that exposure of normal man to pure
O₂ at atmospheric pressures causes pulmonary damage. The longest known voluntary exposure to high oxygen tension lasted 110 hours, and resulted in severe pulmonary dysfunction, with alterations in vital capacity, respiratory rate, minute ventilation, pH, and PaO₂.

It may then be asked whether pulmonary oxygen toxicity is an event of clinical significance in patients who need high concentrations of oxygen for treatment of severe hypoxemia. Evidence that this may be so has accumulated during the last half decade. Before citing them, the reader should be cautioned about the difficulties of interpreting clinical studies. Patients at risk from oxygen toxicity have sufficient pulmonary disease that the administration of high concentrations of inspired oxygen is necessary to provide viable arterial and tissue tensions. The damage from oxygen administration, therefore, is difficult if not impossible to differentiate from the pulmonary abnormalities causing the hypoxemia. Although oxygen toxicity causes radiologic changes, there is no radiographic appearance pathognomonic of oxygen toxicity. Oxygen toxicity cannot, therefore, be considered a legitimate radiologic diagnosis but, at best, only part of a differential. Similarly, it is generally agreed that there is no pathognomonic pathologic lesion in pulmonary oxygen toxicity that allows the diagnosis to be made at postmortem examination. It is virtually impossible to state that oxygen toxicity has occurred in a patient in severe respiratory failure from any of a multiplicity of causes except by inference on the basis of the history and physical findings.

Despite these difficulties, significant evidence indicating that, as expected, oxygen toxicity is important in critically ill patients has been accumulated. In 1967, two significant retrospective studies appeared. Both were reports of pulmonary abnormalities in patients who had been exposed to high oxygen pressures for prolonged periods. Nash, Blennerhassett, and Pontoppidan reported findings in 70 patients who had died after prolonged ventilator therapy. The patients were divided into four groups; those on ventilators for less than ten days with oxygen concentrations below 90 per cent, for more than ten days with O₂ below 90 per cent, for less than ten days with O₂ above 90 per cent, and for more than ten days with O₂ above 90 per cent. Pulmonary abnormalities were quan-
fied and found to correlate with high oxygen administration, and not with the duration of ventilation. This, and subsequent work, induced Nash to write a paper, "Respirator Lung: A Mismomer." He is undoubtedly correct.

In the same year, Northway, Rosen, and Porter reported the effects of high oxygen concentrations in the treatment of respiratory failure in the neonate. They studied 32 infants with respiratory distress syndrome who were ventilated for more than 24 hours with 80 to 100 per cent O₂. There were 13 survivors who had been exposed to high oxygen concentrations for as long as 15 days. In infants surviving more than 150 hours, the authors found a prolongation of respiratory distress and the development of what was called "chronic pulmonary disease." In those who died, administration of high oxygen concentrations continued for as long as 42 days, and postmortem changes were compatible with previous descriptions of oxygen-induced lesions.

Although neither the study by Nash nor that by Northway can directly incriminate oxygen as a cause of pulmonary damage because of the coexistence of severe pulmonary diseases of other etiologies, the comparisons and controls incorporated into their work make it very probable that their thesis—that the pulmonary toxicity of oxygen played an appreciable role in the evolution of the changes observed—is correct. Perhaps the most remarkable finding was the survival of a patient for 42 days on oxygen concentrations approaching one atmosphere. This is far longer than would be predicted from time-pressure tolerance curves derived from studies of human volunteers and animals.

More recently, two important studies which probably are the only careful prospective investigations of the effect of prolonged inhalation of high oxygen tensions in critically ill patients have been reported. Singer et al., studied 40 patients maintained with intermittent positive-pressure ventilation following heart operations with cardiopulmonary bypass. Tidal volumes were maintained at 10–15 ml/kg and P CO₂ were normal. Patients were assigned alternately to one of two groups. One group received an inspired oxygen concentration sufficient to maintain P O₂ between 80 and 100 mm Hg. P O₂ did not exceed 42 per cent. The other group was ventilated with pure oxygen. Measurements were made for calculation of deadspace-to-tidal volume ratio (V D/V T), shunt fraction, and effective compliance. Twenty patients were studied in each group. The mean time of ventilation in the "limited oxygen" group was 21 hours; that of the pure-oxygen group, 24 hours. At the end of that time there were no significant differences between the two groups in any of the variables measured. In addition, two patients were ventilated for four and seven days, respectively, with pure O₂. They also showed no alterations in V D/V T, shunt fraction (Q s/Q L), or compliance. This study clearly shows that, under the clinical conditions studied, no measurable pulmonary dysfunction could be attributed to inhalation of high oxygen concentrations for a mean time of 24 hours. In two patients, no change was seen at four and seven days. These data, gathered in patients with high shunt fractions after cardiac surgery, should be compared with the tolerance data for normal man, described below.

The second prospective study, by Barber et al., concerned ten patients with irreversible cerebral injuries maintained on ventilators. Five were ventilated with air and five with pure O₂. After 30 hours, the oxygen-ventilated group had significantly greater V D/V T values, and after 40 hours, greater Q s/Q L values. In the oxygen-ventilated group, compliances were lower and lung weights greater, but these changes were not statistically significant. Curiously, the two groups could not be differentiated by microscopic examination of the lungs.

Two points should be borne in mind in the interpretation of the latter study. First, pulmonary injury can be induced by damage to the central nervous system. Second, all patients were receiving steroid therapy, and this in itself has been shown to accelerate the development of pulmonary oxygen toxicity in animals. Despite such unavoidable problems, valuable information can be derived from these studies. Singer showed that in patients with preexisting cardiovascular disease, 24 hours of inhalation of pure oxygen produced no measurable pulmonary dysfunction, and two patients showed no effect after exposures...
much longer than that, confirming the experience of others.\(^2\)\(^{17}\) Barber’s work indicates that in patients without pre-existing cardio-pulmonary dysfunction, measurable, significant changes occurred after 30 hours, confirming some of the observations in healthy man.\(^18\)

It is clear that exposure to increased oxygen tension causes pulmonary changes in healthy man.\(^10\) There is a threshold below which there is no evidence of oxygen damage.\(^13\) The rate of the onset of the disease process is proportional both to the tension of oxygen and to the duration of exposure.

Since it is impossible to examine the lungs of normal human volunteers to determine the rate of onset and course of toxicity, indirect measures have been employed. Many have used the onset of symptom formation to describe tolerance curves.\(^28\) The dominant symptom is substernal distress, which begins as a mild irritation in the area of the carina and may be accompanied by occasional coughing. As exposure continues, pain becomes more intense, and the tracheobronchial tree seems outlined by the irritation, which is exacerbated by coughing or deep breathing. This progresses to dyspnea and paroxysmal coughing. These symptoms are severe, and it would seem that patients would complain of oxygen toxicity developed, but the onset of symptom formation is an inadequate warning of oxygen toxicity in the clinical setting because of intubation and sedation. In human volunteers, however, it gives useful information, as seen in figure 2.

There is wide human variability in the onset of symptom formation and more objective criteria have been sought as indicators of the onset of oxygen toxicity. Among the most sensitive is reduction in vital capacity. It has been shown to change during inhalation of between 0.5 and 1.0 atm of oxygen by Comroe \textit{et al.}\(^29\) and at 2 atm by Clark and Lambert-
TABLE 1. Pulmonary Oxygen Tolerance Studies in Healthy Man*

<table>
<thead>
<tr>
<th>Oxygen Partial Pressure (atm)</th>
<th>Ambient Pressure (atm)</th>
<th>Duration of Exposure (Hours)</th>
<th>Number of Subjects</th>
<th>Indices of Pulmonary Oxygen Toxicity</th>
<th>References</th>
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<td>0.26</td>
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* Review of high oxygen tolerance studies derived from normal human volunteers. The circumstances of each experiment are indicated, as are the variables measured. Statistically significant changes are indicated; it is notable that none were seen at inspired pressures below 0.5 atm. Reproduced and modified with permission of Clark, J. M., and Lambersen, C. J.: Pulmonary Oxygen Toxicity: A Review. Pharmacol Rev. 23: 70, 1971.

† Significant change during or after exposure.
THE TOXICITY OF OXYGEN

sen.29 Many other investigators have used this variable to study tolerance. Extensive studies in human volunteers by Clark and Lamber-
sen 18 have led to time-pressure tolerance curves based on vital capacity changes alone. As toxicity progresses, other changes become measurable. Minute ventilation, respiratory rate, compliance, and blood gases have been among the parameters studied. A summary of pulmonary oxygen tolerance studies in human volunteers is given in table 1.

Useful information can be derived from these tolerance studies. Examination of the literature indicates that no measurable changes in pulmonary function or blood-gas exchange occur in man during exposures to less than 0.5 atm even for long periods. It is also apparent that, despite wide variations in human susceptibility, there is no identifiable risk to the administration of pure O₂ at 1 atm for 24 hours. The maximal concentration of oxygen which is tolerated indefinitely is difficult to define, since the time course would be exceedingly long. Further, hematologic and endocrine responses may occur before pulmonary involvement.25,21 The use of a single-gas, low-pressure, pure-O₂ environment in manned spacecraft has produced abundant evidence that a third of an atmosphere of pure oxygen does not produce measurable changes even after hundreds of hours of exposure.20,25 These studies also indicate that it is primarily the pressure, not the concentration of oxygen, which is determinant in the development of toxicity, although the role of inert gas in protection is discussed below.

Pathology and Histology

Animal Studies

The gross pathologic appearances of the lungs of experimental animals post mortem, for long one of the few ways of assessing the severity and extent of oxygen toxicity, are particularly open to artifactual error. Delay in the preparation of material for histologic examination has been shown to be associated with a progressive increase in the extent of pulmonary changes.26 The mechanism is probably that of absorption atelectasis, since N₂ administered to rats in the terminal stages of oxygen toxicity reduces the total changes seen considerably.27 Many experiments have utilized the exposure of animals to oxygen in small hyperbaric chambers, and postmortem decompression of the lungs involves the possibility that disruptive changes may occur due to expansion of gas.

The question arises as to whether intermittent positive-pressure ventilation influences pulmonary pathology in oxygen toxicity. It would appear that IPPV with normal tidal volumes does not adversely affect pulmonary function, but the use of mechanical over-ventilation may do so. In dogs, IPPV with atmospheric air and normal tidal volumes does not alter pulmonary surfactant,29 and other studies have also failed to record any effect of IPPV on oxygen toxicity at 1 atm, using pressure-volume 59 or surface tension 40 measurements.

However, it has been shown that excessively large tidal volumes, sufficient to impair cardiac output, elevated the minimum surface tension in pulmonary extract examined 24 hours after the insult.61 In addition, by morphometric studies of guinea pigs subjected to hyperventilation in a tank ventilator, Forrest 47 described a reduction in alveolar surface area with no change in the alveolar ducts. These changes are consistent with a reduction in pulmonary surfactant and with the demonstration of a decrease in pulmonary compliance following hyperventilation 43 or prolonged IPPV with hyperinflation.41

It seems possible, therefore, that mechanical over-ventilation of the lung might lead to loss of pulmonary surfactant—a hypothesis first proposed by Clements.44,45 Such a change would obviously lead to augmentation of terminal atelectasis in experiments designed to investigate oxygen toxicity.46

A recent, careful study with both light and electron microscopy disclosed no histologic differences between the lungs of adult goats ventilated with and those spontaneously breathing pure O₂ at 1 atm.29

In the clinical context, it is well known that patients with neurologic disease may be ventilated for many weeks or months without evidence of progressive pulmonary impairment. In addition, a retrospective study of adult patients with respiratory failure implicated oxygen but not IPPV.31 It must be concluded,
then, that IPPV does not play an important role in the “respirator lung syndrome.”

Whatever the difficulties that have existed in the past due to the effects of numerous experimental variables on the pathologic picture of oxygen toxicity, it now seems fairly clear that two types of pulmonary changes arise in response to oxygen. Low doses (approximately 0.5 to 0.8 atm) of oxygen are associated with proliferative changes in endothelium and epithelium; this “chronic” type of toxicity is often non-lethal. In contrast to this are the changes produced by exposure to high concentrations of oxygen—“acute toxicity,” which can be divided into two phases, an immediate “exudative” phase and a slightly delayed “proliferative” phase. Acute toxicity was the type described by J. Lorrain Smith, and is characterized by the histologic features of atelectasis, pulmonary capillary congestion, interstitial and alveolar edema, capillary degeneration, and hemorrhage. To some extent, the distinction between the immediate phase, the delayed phase, and chronic toxicity is arbitrary, and these should be regarded as a spectrum of change in response to high P,O,. The extent to which an animal manifests predominantly the acute or chronic features of oxygen toxicity is dependent mainly on the P,O, but this is modified by individual and species variations.

Our understanding of the development of structural changes in oxygen-poisoned lungs has been advanced considerably in the last few years by the application of morphometric methods of quantifying lung damage and the widespread application of electron microscopy. The first and most extensively quoted study of this kind was that of Kistler and colleagues, who studied rats exposed to 99 per cent oxygen at 1 atm. After 48 hours of exposure, when gross evidence of toxicity was apparent, there were signs of capillary endothelial, but not alveolar epithelial, damage. An approximately two-fold increase in the width of the interstitial space as a result of edema and a small quantity of cellular infiltrate were seen. After 72 hours these changes had progressed in extent, with further widening of the interstitial space, extensive destruction of the capillaries, and marked cellular infiltration. Exudate obliterated 65 per cent of the alveoli. Considerable swelling of both capillary and alveolar lining cells was present at this late stage.

Of interest in this work was the clear demonstration that pulmonary capillaries developed degenerative changes at an earlier stage than alveolar epithelium, yet the epithelia and endothelia are structurally similar, suggesting that humoral factors may be involved. In the primate lung, the endothelium also showed changes at an earlier stage than the epithelium, although the greatest destruction occurred ultimately in the epithelial cells. Using the same techniques, the pathophysiologic processes occurring in the primate lung have been followed by Kaplan, Kapanci, and their colleagues. These careful studies are perhaps most analogous to man, and are reviewed in some detail.

During the exposure of monkeys (Macaca mulatta) to 90–100 per cent O, and a P, of 750 mm Hg for 12 days, approximately 50 per cent died of acute toxicity within seven days, and the remainder became “adapted” to the high oxygen tensions and survived beyond that time. It was possible to wean some of the survivors to ambient air, but only by following a regimen of gradually diminishing P,O,. Immediate exposure to air was associated with cyanosis, presumably due to the alveolar proliferative lesions present at this stage.

Animals were examined after two, four, seven, and 12 days of exposure to O, the morphometric measurements are shown in figure 4. After two days, there was slight swelling of the endothelial cells, and a small amount of interstitial edema fluid was present, although morphometric measurements were within the normal range. After four days, there was considerable destruction of alveolar cells, largely of Type I (membranous pneumocytes). There was an increase in thickness of the air–blood barrier, largely due to a 35 per cent increase in endothelial thickness and an increase in interstitial fluid volume, 40 per cent of which represented an increase in edematous tissue.

After seven days of exposure, hyperplasia of Type II alveolar epithelial cells (granular pneumocytes) had led to a marked increase in alveolar thickness, and the Type I cells were almost completely destroyed. The endothelium differed from region to region, with gross variations in thickness. Thus, although morphom-
Fig. 4. Morphometric measurements of the lungs of monkeys exposed to 100 per cent O₂ for 2, 4, 7, and 12 days, showing the change in thickness of the air-blood barrier. C indicates control animals. Reproduced with permission from Kaplan, Y., Weibel, E. R., Kaplan, H. P., and Robinson, F. R.: "Pathogenesis and Reversibility of the Pulmonary Lesions of Oxygen Toxicity in Monkeys. II. Ultrastructural and Morphometric Studies," Laboratory Investigation 20:107, 1969

Reticular interstitial recorded little change in the average capillary width (fig. 4), considerable cell destruction was present.

The swollen interstitial spaces at this stage were altered by an increasing cellularity composed of fibroblasts and leukocytes. After 12 days of exposure, the proliferative changes seen in the granular pneumocytes were accentuated, and there was a reduction in alveolar spaces due to this increase in pulmonary tissue. The air-blood tissue barrier was increased in thickness by approximately 370 per cent.

Figure 4 also shows the results in two monkeys weaned back onto ambient air after eight to 13 days of exposure to oxygen and then sacrificed at 56 and 84 days, respectively. In both animals, considerable restructuring of normal lung architecture had occurred. In the animal exposed for eight days, focal lesions were present in the septa, characterized by increases in the numbers of fibroblasts and collagen fibers, and by thickened alveolar walls containing normal-appearing Type II cells. After 84 days of recovery (preceded by 13 days of exposure), large scars—representing some 7 per cent of the total alveolar tissue—were present in the alveolar septa, surrounded by normal lung, as determined by light microscopy. Arterial blood gases were normal. Electron microscopy, however, disclosed a 28 per cent increase in the thickness of the air-blood tissue barrier.

The studies of Kistler 47 and Kapanci 48 have recorded interesting differences between the responses of the rat and monkey to oxygen. Thus, although endothelial damage was produced in both species, the rat had a greater loss of capillary surface area, associated with a shorter survival time and little, if any, of the proliferative phase of acute oxygen toxicity.
Many of these changes, such as consolidation, edema, alveolar-cell hypertrophy, hyperplasia, degeneration, and desquamation, have been found in various degrees in numerous other studies. In addition, hyaline membranes (comprising a fibrin network entrappping cellular and tissue debris) have been reported surrounding or lining the alveolar cells and ducts, and these are said to resemble lesions in the lungs of infants dying of hyaline membrane disease. It seems likely that in oxygen toxicity these membranes represent a combination of serous and cellular exudation following the initial critical endothelial damage. It also seems that hyaline membranes are more likely to be seen in oxygen toxicity when the survival time is prolonged, and that some species, e.g., guinea pigs and rabbits, manifest these changes more readily than others, such as rats. This point is discussed at greater length in a recent review.

More recently, the ultrastructural changes in oxygen-poisoned lungs have been subjected to greater scrutiny, and the changes seen are in agreement with the cellular responses described above. This exposure of rats to pure O₂ at 1 atm for 36 hours led to the development of vacuolated inclusions close to normal mitochondria of alveolar epithelial cells, while more prolonged exposure (as long as seven days) led to swelling of the mitochondria of Type II alveolar cells. Increased oxygen tolerance produced by prior exposure to oxygen was associated with an increase in the number of lamellar inclusion bodies in Type II cells. In such oxygen-tolerant rats, the Type II cells were most susceptible to oxygen, and neither Type I cells nor endothelial cells showed any change in response to 85% O₂ at 1 atm.

Figure 5 summarizes the pathologic and histologic changes seen in the lungs of animals exposed to high oxygen pressures.

In the acute response to oxygen toxicity, there is considerable variation in the duration and extent of the exudative and proliferative phases. Thus, in monkeys, the exudative phase lasts approximately four days (in response to pure O₂ at 1 atm), and, if death does not occur, is then replaced by the proliferative phase, which is most prominent at 12 days. Rats manifest an exudative stage at 40 to 72 hours. Whether or not an animal develops the exudative or proliferative responses to oxygen depends not only on the PₐO₂ and species involved, but also on the strain, age, and individual susceptibility to toxicity.

Similar considerations apply to the development of chronic oxygen toxicity, which may be
induced either by intermittent exposure to high partial pressures or by chronic exposure to intermediate concentrations.

It should be emphasized that many of the changes of oxygen toxicity are nonspecific. Thus, septal edema, hyaline membranes, and hyperplasia of alveolar lining cells may be produced by radiation, nitrogen dioxide, pneumonia, and cytotoxic drugs.56-60

**Human Studies**

Table 2 summarizes the pathologic findings in patients who received high concentrations of oxygen for prolonged periods and in whom oxygen toxicity is alleged to have been present. The table also lists other possible etiologies, as in most instances the changes are nonspecific and may be associated with the disease or state which necessitated the use of high inspired oxygen concentrations. Most of these studies are retrospective, with the obvious difficulties in interpretation that this produces. In one instance,61 oxygen at hyperbaric pressure was used to treat a young woman who had an anaerobic pelvic infection. She subsequently developed respiratory insufficiency. Although the lungs of the patient were initially normal, a diagnosis of pulmonary oxygen toxicity was complicated by iatrogenic pulmonary edema, septicemia, and convulsions, which developed during the course of treatment.

Another difficulty of interpretation with many of these studies is that pulmonary disease was present prior to treatment with oxygen. Hyde62 studied five patients with "muscle weakness" who were ventilated with pressure-cycled ventilators at concentrations of oxygen higher than 83 per cent. One patient died on the fifth day, and microscopic examination of the lungs revealed increased alveolar lining cells and fibroblastic proliferation. This patient, however, had a primary diagnosis of myasthenia gravis and "pulmonary emphysema." The four survivors all developed roentgenographic changes of diffuse patchy infiltration and widening of the alveolar-arterial oxygen tension difference (A-aD_o2). These changes disappeared on reducing FIO_2 to less than 0.5.

Nash et al.63 felt that they could correlate greater histologic changes with prolonged treatment with high oxygen concentrations. Moreover, they could distinguish two types of changes: an early exudative phase comprising congestion, alveolar edema, intra-alveolar hemorrhage, and hyaline membranes and a late proliferative phase comprising alveolar and interlobular septal edema, alveolar hyperplasia, and fibroblastic proliferation with early fibrosis.

The prospective study by Barber et al.64 indicates that the very changes characteristic of the J. Lorrain Smith syndrome can also be found in patients ventilated with air. Ten patients with irreversible brain damage were randomly allocated into two groups, one ventilated with air and the other with pure O_2. The oxygen group manifested a considerable increase in A-aD_o2 by 50 hours, but this was not apparent in the air group. However, in both groups, microscopic examination of the lungs disclosed intra-alveolar and interstitial edema, atelectasis, congestion, hemorrhage, and bronchopneumonia. Intravascular coagulation was prominent in both groups and hyaline membranes were absent. The authors concluded that although oxygen had adversely affected the lungs, as indicated by the physiologic measurements, they were unable to delineate oxygen toxicity by microscopy. By comparison with primate work, it would appear that 40–50 hours represents an early stage, at which histologic changes of oxygen toxicity become prominent and electron microscopy might have been useful in distinguishing between the two groups.

**Pathophysiology**

There are many descriptions of the visible changes that occur in animals exposed to subconvulsive toxic pressures of oxygen, but there have been relatively few experiments in which physiologic measurements have been made during the development of acute pulmonary oxygen toxicity. In animals, the signs which have been reported include anorexia and lethargy, followed by irregularity of respiration, coughing, and finally gross difficulty in ventilation. Occasionally, fluid or froth has been seen emanating from the trachea. Death from apparent asphyxia is preceded by cyanosis and apnea.65

The physiologic changes occurring during these events have recently been subjected to greater scrutiny. In conscious dogs breathing
<table>
<thead>
<tr>
<th>Reference</th>
<th>Details</th>
<th>Pulmonary Abnormalities</th>
<th>Other Possible Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>174</td>
<td>3 patients, multiple trauma, ( O_2 ) via Bird respirator</td>
<td>Cellular interstitial infiltration, hyaline membranes</td>
<td>Multiple trauma, pulmonary infection, blood transfusions</td>
</tr>
<tr>
<td>175</td>
<td>1 patient, multiple trauma, IPPV &gt; 80 per cent ( O_2 ) for 26 days</td>
<td>Hyaline membranes, interstitial thickening and edema, alveolar cell hypertrophy, fibroblastic proliferation</td>
<td>Pulmonary emboli, chest trauma, staphylococcal sepsis, acute cor pulmonale, blood transfusion</td>
</tr>
<tr>
<td>176</td>
<td>1 patient, drug overdose</td>
<td>Interstitial fibrosis, fibroblastic proliferation, hyaline membranes lining alveoli, ducts and bronchioles, pulmonary emboli and infection</td>
<td>Septicemia, aspiration pneumonia, staphylococcal pneumonia, intravascular coagulation</td>
</tr>
<tr>
<td>177</td>
<td>Patients in ICU, ( O_2 ) varying</td>
<td>Alveolar edema, alveolar phagocytes, hyaline membranes not convincingly related to ( F_{O_2} )</td>
<td>Pulmonary infection, aspiration, cerebrovascular disease, pulmonary emboli, chronic pulmonary disease</td>
</tr>
<tr>
<td>61</td>
<td>Patient with anaerobic infection treated with hyperbaric oxygen</td>
<td>Congestion, edema, hyaline membranes</td>
<td>Septicemia, blood transfusions, induced iatrogenic pulmonary edema, convulsions, air embolus</td>
</tr>
<tr>
<td>178</td>
<td>50 air crew with &gt; 500 hours of jet flight killed in accidents compared with young adults who died of multiple trauma</td>
<td>Higher incidence than control lungs of thickened alveolar septa and prominence of capillaries</td>
<td>Multiple trauma, Not known whether air crews had greater thoracic trauma than control group</td>
</tr>
<tr>
<td>179</td>
<td>2 patients, cerebrovascular disease, multiple trauma, IPPV with high ( O_2 )</td>
<td>Hyaline membranes, intra-alveolar hemorrhage, alveolar cell hyperplasia, alveolar edema</td>
<td>Cerebrovascular disease, chest trauma, blood transfusions</td>
</tr>
<tr>
<td>180</td>
<td>Shocked patients who have received high ( O_2 )</td>
<td>Hyaline membranes, pulmonary edema</td>
<td>Pulmonary emboli, pulmonary infection, congestive heart failure</td>
</tr>
<tr>
<td>62</td>
<td>5 patients with muscle weakness, &gt; 83 per cent ( O_2 ) via respirator; 1 patient died</td>
<td>Septal thickening, alveolar cell hyperplasia, fibroblastic proliferation</td>
<td>Pulmonary infection, chronic pulmonary disease</td>
</tr>
<tr>
<td>181</td>
<td>38 patients, multiple diseases, IPPV &gt; 40% ( O_2 ); death in 3-120 days</td>
<td>Intra-alveolar fibrosis, hyaline membranes, alveolar thickening, fibroblastic proliferation, prominent alveolar lining cells</td>
<td>Many associated diseases, including head injury, chronic pulmonary disease, aspiration pneumonia, pulmonary infection, congestive heart failure</td>
</tr>
<tr>
<td>11</td>
<td>70 patients divided into 4 groups; the lungs of those ventilated with 90-100% ( O_2 ) for &gt; 10 days had the greatest changes</td>
<td>Congestion edema, hemorrhage, fibroblastic proliferation</td>
<td>Post-cardiac surgery, pulmonary infection, chronic pulmonary disease</td>
</tr>
</tbody>
</table>
### Table 2. (Continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Details</th>
<th>Pulmonary Abnormalities</th>
<th>Other Possible Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>Infants with respiratory distress syndrome (hyaline membrane disease) treated with 80-100 per cent O₂ for &gt; 10 days</td>
<td>Death in 2 days with typical RDS picture; survival for 10 days associated with fewer hyaline membranes; alveolar cell hyperplasia, interstitial edema, thickened basement membranes; arteriolar hypertrophy</td>
<td>Hypoxia, HIDS</td>
</tr>
<tr>
<td>115</td>
<td>10 patients with O₂ therapy for one hour for 7 days, FIO₂ unknown</td>
<td>Capillary congestion and capillary proliferation; thickening of septal cells with fibrocyte proliferation</td>
<td>Cardiovascular disease, congestive heart failure, chronic pulmonary disease</td>
</tr>
<tr>
<td>37</td>
<td>47 cases, many diseases, FIO₂ unknown</td>
<td>The longer the duration of O₂ therapy, the higher the amount of capillary proliferation</td>
<td>Infection, trauma</td>
</tr>
<tr>
<td>182</td>
<td>6 patients, non-thoracic trauma, FIO₂ unknown</td>
<td>Septal thickening, hyaline membranes, capillary hyperplasia</td>
<td>Pulmonary infection, pulmonary emboli, multiple pulmonary infarction</td>
</tr>
<tr>
<td>183</td>
<td>6 patients, IPPV with 100% O₂ for 2-11 days</td>
<td>Hypertrophy of lining cells, interstitial and alveolar edema, hyaline membranes, fibroblastic interstitial proliferation; no capillary proliferation</td>
<td>Shock, repeated cardiac arrests, acute cor pulmonale, blood transfusions post-cardiac surgery</td>
</tr>
<tr>
<td>24</td>
<td>1 patient &gt; 60% O₂ for 7 days</td>
<td>Hyaline membranes, interstitial fibrosis, mononuclear infiltrate; dilated capillaries</td>
<td>Post-cardiac surgery, blood transfusions</td>
</tr>
</tbody>
</table>

100 per cent O₂ at 1 atm for 55 hours (mean survival time), Smith *et al.* found little change in respiratory or cardiovascular variables until the terminal stages of oxygen toxicity, at which time there was a decrease in arterial oxygenation and cardiac output. In a similar study of anesthetized dogs spontaneously breathing pure O₂ at 2 atm, there were no changes in pulmonary shunt ratio until five hours before death, which occurred at a mean time of 18 hours. In the former study death appeared to result from asphyxia, while in the latter, in four of the six animals, arterial oxygenation was reported in excess of 75 per cent saturation in the terminal stage, and respiratory failure and cardiovascular collapse were implicated in the mechanism of death.

The immediate physiologic responses seen in the cardiovascular system after the introduction of 100 per cent O₂ in the inspired gas have been well documented. An increase in systemic vascular resistance occurs in response to hyperoxia, concomitant with a decline in cardiac output, the net result being to leave the mean systemic blood pressure unchanged. Apart from the demonstration of systemic hypertension in rats exposed to oxygen at 3 atm, these physiologic changes in response to hyperoxia do not progress, but are maintained until the terminal stages of oxygen toxicity. Hyperoxia has been shown to produce an increase in pulmonary arterial pressure, and suggestive confirmatory evidence is provided by the histologic demonstration of pulmonary arterial and arteriolar thickening and hypertrophy. However, the changes in pulmonary arterial pressure in dogs appear to be of relatively low magnitude—an increase of 4 mm Hg in 40 hours was reported at 1 atm, while at 2 atm changes of 6 mm Hg in nine hours, 4 mm Hg in 12 hours, and 5 mm Hg in eight hours have been recorded. A consistent finding in many animal studies is reduced pulmonary compliance. Whether such a change in compliance would occur in the absence of mechanical alterations...
such as atelectasis, congestion, and edema is unknown. A decline in dynamic pulmonary compliance in man in the absence of such changes has been reported.\(^7\) Atelectasis and edema were ruled out by the absence of radiologic evidence or alteration in the A-a\(\mathrm{D}_\text{O}_2\), and pulmonary congestion by the absence of a measurable increase in pulmonary tissue volume or pulmonary capillary blood volume.\(^7\)

The exposure of human volunteers to high oxygen pressures has permitted measurement of altered respiratory function many hours before the development of anatomic changes or irreversible toxicity. The rate of development of severe symptoms is quite variable, and subjective reports may be delayed until measured changes have occurred in lung function, particularly changes in vital capacity.\(^9\) Caldwell et al.\(^9\) showed that in every subject exposed to 98 per cent \(\mathrm{O}_2\) at 1 atm, vital capacity continued to decline after the chest pains had disappeared, suggesting that subject discomfort was not the primary cause of such a change.

Several investigations have demonstrated that oxygen breathing is accompanied by a decline in vital capacity,\(^5,10,19\) In Caldwell's study,\(^10\) the VC of one subject decreased 35 per cent after 74 hours of exposure, and several weeks elapsed before the pre-exposure value was restored. Radiologic examination of the chest of this subject showed no changes, and he had an A-a\(\mathrm{D}_\text{O}_2\) of 59 mm Hg. This compares well with an average A-a\(\mathrm{D}_\text{O}_2\) in six subjects of 46 mm Hg after 0.5 hours of breathing \(\mathrm{O}_2\) at 1 atm.\(^5\) In Caldwell's subject the cause of the impairment in vital capacity was not established, but on the basis of associated decreases in diffusing capacity beginning at 48 hours it was proposed that early alveolar edema formation had occurred. How-
ever, the absence of radiologic changes and low A-accretion make this explanation unlikely.

Clark and Lambert suggest that the diminution of vital capacity represents the best index of the development of oxygen toxicity in man.

The lower half of figure 6 shows the reductions in mean vital capacity of 11 subjects breathing oxygen through tightly-fitting rubber face masks. In most instances, the subjects had undergone cannulation of the femoral artery. The upper half shows a curve representing the rate of development of symptoms. Although there was considerable variation in the rates at which symptoms developed, the decrease in vital capacity occurred before they were prominent. Unfortunately, because control values of vital capacities of these subjects breathing air under the same conditions are not available, we do not know to what extent mask breathing and arterial cannulation contributed to these changes. However, in a similar study of ten subjects at 2 atm, which was terminated after five hours, there were no reported changes in vital capacity, and symptoms referable to pulmonary irritation were not prominent.5 This may reflect both individual variation and the difficulty of measuring a 5 per cent change in vital capacity. The importance of vital capacity is that it represents the only currently useful measurement of the rate of development of oxygen toxicity in patients with previously-normal lungs.

In the studies of Clark22 and Caldwell23 the changes in vital capacity followed the same pattern. Following termination of exposure, vital capacity continued to decline, and recovery to pre-exposure values took an average of one to three days.

Atelectasis has been implicated as the mechanism whereby a decrease in vital capacity is induced in oxygen toxicity.52 However, in prolonged studies of volunteers exposed to oxygen at 1.0 atm 19,20 or 2 atm,2 no radiologic evidence of change has been encountered, and the A-accretion appears to be relatively stable, so it seems unlikely that collapse of the lung plays a significant part, apart from those situations in which airway gas trapping occurs.52

It is interesting that the reduction in vital capacity seems to occur mainly at the expense of the inspiratory reserve volume, implicating as a possible mechanism muscle weakness due to fatigue and discomfort and, when present, retrosternal soreness induced by deep inspiration.22

Other changes observed in man include abnormalities in compliance,19,20 diffusing capacity,24 pulmonary capillary blood volume,44 and airway resistance.81 Decreases in dynamic pulmonary compliance after 30 hours of O2 at 1 atm 19 and five hours after an 11-hour exposure to 100 per cent O2 at 2 atm29 have been reported. These changes are not related to the decrease in compliance produced by absorption collapse, which is readily reversed by deep breathing.52 An explanation for the changes in compliance in the early stages of oxygen toxicity seen in volunteers is elusive, because atelectasis, pulmonary edema and congestion have not been seen.

Reported changes in pulmonary diffusing capacity (DLCO)15,54 reflect the technical difficulties of performing and interpreting these measurements under conditions of breathing oxygen. A significant decrease in DLCO after breathing O2 at 1 atm for three hours has been reported,55 but this was not subsequently confirmed.57 After exposure to 95 per cent O2 for 30–74 hours, DLCO decreased by 19 per cent,70 and after exposure to 100 per cent O2 at 2 atm for 6–11 hours, DLCO decreased by 16 per cent.44 Hence, it seems likely that if any changes take place, they occur only after prolonged exposure.

The results of measurement of pulmonary capillary blood volume conflict similarly. Caldwell19 found no changes after prolonged exposure of subjects to 95 per cent O2 at 1 atm, while Fuy and his colleagues found a 50 per cent decrease after 6–11 hours of oxygen at 2 atm.44 Different results were found by Rosenberg and MacLean,57 who observed men breathing oxygen at 1 and 3 atm for as long as three hours. With hyperbaric but not atmospheric oxygen, an increase in the ratio of DLCO to V̇E in every subject was found, and this was interpreted as evidence of an increase in pulmonary capillary blood volume.

Airway resistance (Rair) has been found either to decrease as1 or to remain unchanged in response to breathing oxygen at 2 atm. However, in the latter study, measurement of Rair was not made until 3–5 hours after ad-
ministration of $O_2$ was discontinued. In the study of Smith and colleagues, $R_{aw}$ was measured immediately after discontinuing oxygen inside a pressure chamber, and a significant reduction in specific airway conductance was found. Whether this response was vagal in origin or resulted from a direct effect on bronchiolar smooth muscle was not determined.

Mechanisms of Pulmonary Oxygen Toxicity

The concern of clinicians and the dramatic effects of oxygen toxicity have led to a detailed consideration of the pathophysiology produced. This should not be allowed to obscure the fact that oxygen toxicity is fundamentally a biochemical phenomenon of great complexity. The voluminous literature on the biochemical effects of increased oxygen at cellular and subcellular levels has been extensively reviewed: the reader is referred to the works of Haugaard, Davies and Davies, and Gerschman. Haugaard prefaxes a discussion of the topic by stating that "... although $O_2$ is necessary for the production of energy and survival of all aerobic cells, it is also a universal cellular poison. It is only because cells in the course of evolution have developed special defense mechanisms against the toxic effect of $O_2$ that life as we know it has been able to flourish. In a sense, the study of $O_2$ toxicity is the study of the ways in which organisms protect themselves against the oxidizing potential of molecular $O_2$. Thus, it is likely that fundamental understanding of the ubiquitous physiologic manifestations of oxygen toxicity will come about only through additional knowledge of the biochemical basis for the process. Attempts to protect against oxygen toxicity by modifying specific biochemical events have been made. These have not yet proven clinically useful, but it is likely that if true protective measures can be found, it will be through such specific and basic investigations.

Most research on the biochemistry of oxygen toxicity has been done with isolated enzyme systems and tissue preparations in vitro. It should be borne in mind that the oxygen tensions produced in such preparations are far higher than at analogous sites of action in vivo. Thus, extrapolations to the intact organism must be made with caution. Parenthetically, the tissue with the highest intracellular oxygen tension is the lung, where $P_{O_2}$'s in alveolar and capillary cells are a function of the alveolar concentration, the tension in blood, and the metabolic demands of the cells. Small wonder that under normobaric conditions, the lung is the first organ to manifest oxygen damage.

Although there is great variability in enzymatic resistance to oxygen toxicity, many reactions are very sensitive and easily inactivated. Among those which have received much attention are those containing SH groups, the sulfhydryl enzymes. Several mechanisms for the oxidation of SH groups have been proposed, and it is not yet known which pathways are involved. One view concerns the formation of free radicals, and is supported by the observation that trace metals, notably ionic forms of iron and copper, are essential for SH-group oxidation. Another view supports the involvement of a dual role played by glutathione. Oxidation of glutathione allows it to react with the SH groups of sulfhydryl enzymes, inactivating them, and resulting in final formation of $H_2O_2$, which can then be degraded by catalase. On the other hand, it has been demonstrated that reduced glutathione (GSH) may serve to re-activate some oxidized sulfhydryl enzymes. Inactivation of SH enzymes can have profound effects at many sites of action. Several such enzymes are involved in the tricarboxylic acid cycle. An enzyme essential to glycolysis, glyceraldehyde phosphate dehydrogenase, is susceptible to oxidation. In cellular respiration, several flavoproteins are particularly vulnerable, and Chance et al. have demonstrated that oxygen interferes with the chain of electron transport in this system. Oxygen may interfere with oxidative phosphorylation in the mitochondria. Other investigations have demonstrated the altered metabolism of glutamate and GABA, which may be fundamental to the CNS effects of oxygen at high pressure. Lipid peroxidation may also be important in the mechanism of oxygen toxicity. At present, although a great variety of agents has been used to attempt to modify oxygen toxicity, none has proven of clinical utility.
There is abundant evidence that the rate of development of oxygen toxicity is primarily dependent upon the inspired oxygen level and the duration of exposure. However, the work of Bean and others clearly demonstrates that many other factors are significant in the rate of development of toxicity. Since sympathoadrenomedullary and hypophysial-adrenocortical pathways are known to be involved, the question of the relative importance of alveolar versus arterial oxygen tensions is an important one. The time-pressure tolerance relationships discussed above have all been determined from normal volunteers in whom there is no evidence of the gas-exchange dysfunctions which commonly characterize patients exposed to high oxygen tensions. There is some evidence that patients in respiratory failure have survived oxygen exposures vastly in excess of what the tolerance curves would predict.

That direct toxic effects of hyperbaric oxygen can damage lung tissue was demonstrated in 1958 by Penrod, who ventilated anesthetized cats through a double-lumen catheter at 5 atm. One lung was exposed to oxygen and the other to inert gas. After exposure for seven hours, the oxygen-ventilated lung contained severe gross and microscopic changes compatible with oxygen toxicity, while that ventilated with inert gas did not. This observation has subsequently been confirmed under other experimental circumstances, and the importance of a direct toxic effect clearly established, despite the increased A-aD O₂ created by ventilation of the two lungs with different oxygen concentrations.

The question of whether a large A-aD O₂, commonly found in patients in ventilatory failure, alters the rate of development of oxygen toxicity was first addressed by Winter et al. An anatomic veno-arterial shunt was created in dogs such that after a recovery period of two weeks they had a mean PaO₂ of 40.7 mm Hg while breathing air. Animals were exposed to oxygen in three groups: normal controls exposed to 2.5 atm for a mean time of 5.1 hours, then to 2.0 atm until death; shunted animals exposed according to the same regimen, and shunted animals exposed to the mean time of death of the controls. Normal animals died after 12.3 hours on this regimen, while shunted animals survived for a mean time of 21.1 hours. Gross and histologic examinations showed severe pulmonary damage in the groups exposed until death, with no difference between the shunted and unshunted animals. However, the third group, shunted animals sacrificed at the mean time of death of the control group, had only minimal pulmonary damage.

In a complex series of experiments, Thomas et al demonstrated the importance of the bronchial circulation and pulmonary venous oxygen tension in the development of chronic oxygen toxicity. In one group of dogs, the right pulmonary artery was ligated, and sufficient time was allowed for development of collateral bronchial vessels. In another, the lung was anastomosed to the left atrium, producing an increased A-aD O₂. Following recovery, the right middle pulmonary artery was ligated and time again allowed for development of collateral flow. Exposure was intermittent, four one-hour periods per day at 3 atm, for a total of 120 exposures. There was no seizure activity, nor was there evidence of respiratory distress during this regimen. The most severe damage was seen in the right lung of the noncyanotic group—the side in which there had been pulmonary-artery ligation and an increase in bronchial circulation. Marked fibrosis, increased cellularity of alveolar membranes, and increased vascularity were found. In the cyanotic group, the lobe that had had pulmonary-artery ligation showed slight alveolar proliferative changes, while the left lung showed no appreciable abnormality. Thus, in both groups, damage was greater in the side being perfused with the augmented bronchial arterial circulation. Both degree of abnormality and increases in minimum surface tension of lung extract correlated with pulmonary venous oxygen tensions from the corresponding lobe. The higher the venous effluent oxygen tension, the greater the abnormalities and the presumed decrease in surfactant.

These two studies seem to indicate that systemic oxygen tension and the oxygen tension perfusing the lung exert effects on the rate of development of pulmonary toxicity. Both, however, were performed at hyperbaric pres-
sures, and subsequent research at normal pressures appears to refute the findings.

Miller et al.\textsuperscript{107} created large intracardiac right-to-left shunts in dogs that resulted in arterial oxygen tensions of 29 to 58 mm Hg during breathing of air. Cyanotic dogs and control animals not subjected to operation were exposed to 98–100 per cent O\textsubscript{2} for 48 hours and then sacrificed, no attempt being made to determine survival time. Surface tension and pulmonary damage were then investigated. It was found that there were no observable differences between the two groups, surface tensions being abnormally high in both, and pulmonary damage not detectably greater in the cyanotic group. That P\textsubscript{aO\textsubscript{2}}'s in both groups were essentially unchanged at the time of sacrifice indicates that the animals were not in the terminal stage of oxygen toxicity. No detailed description of the pathologic changes or their methods of quantification is given, but the evidence of Miller and his co-workers suggests that an increased A-aD\textsubscript{O\textsubscript{2}} does not provide protection at normobaric levels of oxygen.

A confirmatory study has recently been done by Ashbaugh.\textsuperscript{106} He diverted inferior vena caval blood flow into the left atrium in 11 dogs. These, and ten control animals, were exposed to 540–580 mm Hg, or approximately three quarters of an atmosphere of oxygen, until death. Daily measurements of blood gases, arterial oxygen saturation, systemic and pulmonary arterial pressures, cardiac output, and serum enzymes were made. There were no significant differences between survival times (8.2 days for hypoxicemic and 8.25 days for normal dogs), degrees of pulmonary changes, or other variables observed. Of the 21 dogs exposed, eight showed only slight symptoms in the early stages of exposure. This group survived a mean time of 11.1 days, while those showing early distress died at 5.4 days. This careful study confirms the work of Miller,\textsuperscript{106} and indicates that a large A-aD\textsubscript{O\textsubscript{2}} does not appear to alter the rate of development of oxygen toxicity at atmospheric exposure pressures. The unusually long survival times of Ashbaugh's animals were probably the result of the relatively low inspired oxygen tension. Of considerable interest, as he points out, was the marked individual variability of the experimental animals, with some surviving for as long as 14 days, while others died in three. The reason is unknown, and its elucidation of potential importance. The relatively low oxygen tension used may have allowed resistant animals to progress from the exudative to the proliferative stage of pulmonary damage, with consequent increases of survival times, as had been reported by others working at subatmospheric exposures.\textsuperscript{109}

The conclusion that must be drawn at present from these four studies is that large A-aD\textsubscript{O\textsubscript{2}}'s protect against both the CNS and pulmonary manifestations of oxygen toxicity at hyperbaric exposure levels, but do not protect the lungs during exposures to oxygen at 1 atm or less. This leaves unexplained the occasional long tolerance to oxygen found in critically ill patients, but at present no support can be given to the concept that a normal or low systemic oxygen level protects against oxygen toxicity in the clinical setting.

Another study of great interest is that of Brauer et al.,\textsuperscript{119} who investigated the relationship between acclimatization to altitude and the rate of development of pulmonary oxygen toxicity. Rats of standard weight were exposed to air at a total pressure of 380 mm Hg, an altitude equivalent of 17,400 feet, for eight weeks. The calculated P\textsubscript{A\textsubscript{a}} produced was approximately 40 mm Hg. Following the exposure to altitude, the animals were subjected to an environment consisting of 818 mm Hg O\textsubscript{2} and slightly more than 700 mm Hg N\textsubscript{2}. Altitude-acclimatized rats were exposed with unacclimatized controls. Normal rats had a mean survival time of 51 ± 3 hours before dying of pulmonary oxygen toxicity; altitude-exposed rats survived the high-oxygen-tension environment for 188 ± 49 hours. This more-than-threefold increase in survival time represents the greatest protection yet afforded against pulmonary oxygen toxicity by an experimental manipulation. When acclimatized animals were returned to sea level for various periods prior to exposure to oxygen, the protective effect decreased, but it persisted for as long as 30 days. In contrast, the polycythemia of altitude had reverted to normal after 11 days. When altitude-acclimatized rats were compared with controls in their responses to acute high-pressure oxygen exposure (7 atm),
no protection against CNS toxicity was observed.

This study indicates that some aspect of acclimatization to altitude, one which apparently persists after the hypoxic exposure, affects the response to toxic oxygen levels. It is worth recalling that the experimental animals of Winter, Miller, and Ashbaugh all had been functionally exposed to high altitude, in that their Pao\textsubscript{2}'s had been lowered by surgically induced venous admixture, and that this had persisted during recovery periods ranging from two weeks to several months. Clearly, no solutions are suggested by the provocative work of Brauer, but further investigations are indicated.

The indirect mechanisms whereby oxygen affects the lungs have been demonstrated largely by maneuvers intended to modify the time course of the response to oxygen. This applies particularly to the demonstration of the roles of hypophyseal-adrenocortical and sympatho-adrenal interactions, thyroid activity, lactate, and carbon dioxide. In addition, myocardial depression and surfactant inhibition have been implicated in the pathogenesis of pulmonary oxygen toxicity.

**Absorption Collapse**

There can be little doubt of the importance of the phenomenon of collapse of the lung during breathing of oxygen, but evidence for this event as an initiating factor in the development of acute pulmonary oxygen toxicity is tenuous.

Collapse of alveoli during breathing of oxygen has been demonstrated in a variety of situations where partial or complete occlusion of the airways occurs. Thus, it takes place in the presence of high gravitational forces, at reduced lung volumes, at low lung volumes in the presence of demonstrable airway closure, and at normal lung volumes in the absence of coughing or sighing. It must be presumed that in patients with pulmonary disease, including narrowing of the airways resulting from mucus retention, inflammation, or other conditions, collapse may occur more readily with breathing of oxygen than in healthy patients. In the clinical management of patients who receive high concentrations of oxygen, particular attention should be given to maneuvers which help to maintain the patency of airways, including physiotherapy of the chest and high tidal volumes to increase FRC by the use of positive end-expiratory pressures.

A search of the literature describing the pulmonary damage caused by oxygen toxicity consistently reveals descriptions of gross atelectasis, suggesting that collapse is an important factor in this condition. However, it has been found that the degree of consolidation increases with the amount of delay between terminal apnea and fixation of the lungs. Therefore, the atelectasis seen may result from postmortem, not antemortem, changes. Consistent with this hypothesis has been the demonstration that in the terminal stages of oxygen toxicity apnea may precede cardiovascular collapse. There is no evidence in animals to support the view that progressive alveolar collapse occurs, since the A\textsubscript{a}DO\textsubscript{2} remains stable until the terminal stages of acute pulmonary oxygen toxicity. It must be concluded that collapse of the lung, although present in the late stages of pulmonary oxygen toxicity, is largely a resultant and not an initiating event.

**Pulmonary Surfactant**

The importance of the surface tension of alveoli in maintaining their patency was realized by von Neergard in 1929. The prevention of transudation of fluid into the alveolar lumen was an additional function stressed by Pattle. As edema and atelectasis were identified as features of pulmonary oxygen toxicity, it was natural for investigators to turn their attention to the effects of oxygen on pulmonary surfactant.

There have been many studies of the effects of oxygen at hyperbaric or atmospheric pressure on lung surfactant, some with negative results, others showing reduced surfactant activity. Many methods of estimating surfactant activity have been utilized. Some are open to question, in particular those involving examination of lung extracts and the correlation of such results with the state of the alveolar lining in vivo. In addition, the interpretation of measured changes in surfactant activity is difficult, since many factors, such as contamination with serum or fibrinogen, cholinergic stimulation, and perhaps me-
Mechanical overventilation of the lungs,\textsuperscript{44} are known to diminish it. Pulmonary edema is associated with mechanical changes in the lungs\textsuperscript{126} caused by increased surface tension in the edematous parts.\textsuperscript{127}

Although it seems certain that there are measurable changes in surface tension in the late stages of acute pulmonary oxygen toxicity, it is not clear whether these are the result of direct effects or indirect effects consequent upon mechanical changes induced by oxygen.

Type II alveolar epithelial cells are thought to be the source of surfactant.\textsuperscript{125,129} In a study of anesthetized dogs ventilated through a double-lumen tube at 1 atm,\textsuperscript{194} one lung with air, the other with oxygen, there was a greater diminution in surfactant activity in the oxygen-ventilated lung than in the air-ventilated lung. A similar correlation existed with regard to reductions in the number of Type II alveolar cells and the number of lamellae contained in these cells. This work should be contrasted with the results reported by Kapanic et al.,\textsuperscript{48} in which little reduction in the number of Type II cells in the conscious monkey was found.

Although hyperplasia of Type II cells in the later stages of acute pulmonary oxygen toxicity is well documented,\textsuperscript{48} any relationship between such changes and reduced surface tension is speculative at the present time.

**Myocardial Failure**

The similarity between the edema of acute pulmonary oxygen toxicity and that of left ventricular failure raises the question of myocardial involvement.

Experiments \textit{in vivo} have revealed that myocardial metabolism may be depressed by oxygen. Glyceraldehyde phosphate dehydrogenase in heart homogenates was inactivated by oxygen at 1 atm,\textsuperscript{54} and glucose and pyruvate metabolism were also depressed by oxygen in homogenates of rat heart.\textsuperscript{120} However, postmortem examination of the hearts of rats exposed intact to oxygen at 5 atm for three hours before death revealed no changes at ATP concentration or oxygen consumption of the homogenized heart, but a slightly increased production of lactic acid was observed.\textsuperscript{121} In the intact preparation, exposure of anesthetized dogs to brief (30-minute) periods of oxygen at 3 atm was accompanied by a change in myocardial utilization of substrates, and oxygen consumption was significantly depressed. This was thought to reflect the marked reduction in myocardial blood flow and a decreased demand by a heart performing less work rather than toxicity of oxygen, although the possibility of such a change could not be ruled out.\textsuperscript{122}

This relative paucity of biochemical data does not assist in the interpretation of the conflicting physiologic measurements derived from studies designed to elucidate the contribution of myocardial failure in oxygen toxicity.

In open-chested dogs, alteration of the inspired gas from air to pure O\textsubscript{2} at 1 atm was associated with cardiac dilation and a reduction in ventricular isometric systolic tension, changes which could be explained as facets of early oxygen toxicity.\textsuperscript{123} Oxygen toxicity has also been invoked to explain the diminished contractility of the guinea pig heart.\textsuperscript{124}

Persistent severe hypertension has been found in the rat exposed to hyperbaric pressure by some investigators, and the pulmonary edema of oxygen toxicity has been ascribed to acute left ventricular failure.\textsuperscript{70} The same workers also reported systemic hypertension in dogs,\textsuperscript{70} but this has not been a feature of other reports.\textsuperscript{55,71,122,125}

There have been few studies in which cardiovascular variables have been followed for prolonged periods to and including the development of pulmonary oxygen toxicity. Clarke et al., using anesthetized dogs breathing spontaneously, found marked reductions in cardiac output in the terminal stages of pulmonary oxygen toxicity at 2 atm in four of six, and interpreted this as evidence of myocardial failure.\textsuperscript{125} However, Smith et al.,\textsuperscript{62} were unable to demonstrate any changes in left atrial pressure in conscious dogs breathing oxygen at 1 atm for 50 hours.

In summary, although there is conflicting evidence, it is not likely that myocardial failure leads to the edema seen in acute pulmonary oxygen toxicity at normal baric pressure.

**Inert Gas and CO\textsubscript{2}**

The role of N\textsubscript{2} in the development of absorption atelecctasis has been discussed above.
THE TOXICITY OF OXYGEN

Table 3. Effects of Inert Gas on Pulmonary and Central Nervous System Oxygen Toxicity

<table>
<thead>
<tr>
<th>Reference</th>
<th>Species</th>
<th>Total Pressure (atm)</th>
<th>Inert Gas Pressure (atm)</th>
<th>Oxygen Pressure (atm)</th>
<th>Effect*</th>
</tr>
</thead>
<tbody>
<tr>
<td>138</td>
<td>Man</td>
<td>4.0</td>
<td>2.0 N₂</td>
<td>2.0</td>
<td>↓C</td>
</tr>
<tr>
<td>184</td>
<td>Rats</td>
<td>6.0</td>
<td>3.0 N₂ or 3.0 He</td>
<td>3.0</td>
<td>→→C &amp; P</td>
</tr>
<tr>
<td>185</td>
<td>Rats</td>
<td>1-3.0</td>
<td>0-4.0 N₂ or 3.0 He</td>
<td>1.0</td>
<td>→→P</td>
</tr>
<tr>
<td>187</td>
<td>Rats</td>
<td>53.3</td>
<td>48 He</td>
<td>5.3</td>
<td>↓C</td>
</tr>
<tr>
<td>186</td>
<td>Mice</td>
<td>6.2 or 8.8</td>
<td>2.2 N₂ or 4.8 N₂</td>
<td>4.0</td>
<td>↑↑C</td>
</tr>
<tr>
<td>187</td>
<td>Dogs</td>
<td>3.0</td>
<td>1.0 N₂</td>
<td>2.0</td>
<td>↑↓P</td>
</tr>
<tr>
<td>139</td>
<td>Rats-mice</td>
<td>3.0</td>
<td>1.0 N₂</td>
<td>2.0</td>
<td>↑↓P</td>
</tr>
<tr>
<td></td>
<td>Rats-mice</td>
<td>3.0</td>
<td>1.0 CO</td>
<td>2.0</td>
<td>↑→P</td>
</tr>
</tbody>
</table>

* Key:
- C = CNS oxygen toxicity
- P = pulmonary decrease in tolerance
- ↑ increase in tolerance
- → no change in tolerance

However, in addition, nitrogen may modify oxygen toxicity in other ways. Table 3 shows some of the results of experiments designed to investigate the effects of inert gases on mammals exposed to oxygen. It may be seen that inert gases may enhance, delay, or have no effect on the rate of onset of central or pulmonary oxygen toxicity. This paradox may be explicable in the light of the fact that inert gases may modify oxygen toxicity in several ways: by a central effect, i.e., a narcotic or anesthetic type of action which is predominantly manifest at high pressures; by increased gas density, which leads to a decrease in alveolar ventilation and an increase in arterial PaCO₂, which may in turn influence the development of oxygen toxicity as described below; and by affecting the local response of the lung tissue to hyperoxia. At present, available data are insufficient to sort out the relative contributions of these mechanisms.

However, it is clear from the aerospace research programs that man may tolerate a nitrogen-free environment for many weeks without untoward effects, supporting the concept that at subatmospheric pressures the response to oxygen is dependent more on partial pressure than concentrations.

It has been known for many years that carbon dioxide influences oxygen toxicity. With an increase in venous oxygen saturation, there is a loss in buffering capacity of the blood. A subsequent decrease in tissue pH and increase in tissue PaCO₂ was suggested by Gesell as a mechanism for oxygen-induced convulsions. However, the suggested changes in brain PaCO₂ are of relatively low magnitude, ranging from 2.5 to 6.0 mm Hg, and it is the consensus that this order of change plays a contributory role, but is not directly responsible for oxygen-induced convulsions.

Although there is considerable documentation that variations in inspired PaCO₂ affect oxygen toxicity at high pressures, there is no convincing evidence that CO₂ influences the development of pulmonary oxygen toxicity at atmospheric pressures.

ROLE OF THE ENDOCRINE SYSTEM

The general rate of metabolism has been found to affect the responses to oxygen toxicity. In several species, such as the rat and ground squirrel, a correlation between mortality rate and oxygen consumption has been found. Faulkner and Binger found that poikilotherms appear more resistant to oxygen toxicity than homeotherms.

It is not surprising then that the thyroid gland affects the rate of development of pulmonary oxygen toxicity. Thus, thyroxine or thyroid extract has been shown to hasten the onset of both convulsions and pulmonary damage in cats at hyperbaric pressures of oxygen. Even at pressures of 0.9 to 1 atm of oxygen, thyroxine augments the onset of toxicity in both normal and hypophysectomized...
Conversely, depression of cellular metabolism by anesthesia or hibernation is associated with a reduction in susceptibility to pulmonary oxygen toxicity. Part of the protective effect of hypophysectomy against pulmonary oxygen toxicity may be owing to a reduction in TSH secretion, but adrenocortical hormones are also known to be implicated in the development of oxygen toxicity, so a reduction in ACTH secretion represents a second route whereby hypophysectomy affords protection. This effect is demonstrable at pressures of 0.9 to 1 atm in rats, so it is not necessary to implicate an interaction between convulsive CNS activity and hypophyseal response. At ambient pressures, prolongation of the development of pulmonary damage is afforded by adrenalectomy in rats exposed to 100 per cent O₂, while conversely cortisone and similar adrenocorticoids augment the rate of development of pulmonary damage. There is considerable documentation of similar effects by cortisone and adrenalectomy at hyperbaric pressures of oxygen. Although these data cannot be extrapolated directly to man, the common practice of administering corticosteroids to those patients at risk from oxygen toxicity in order to reduce "inflammation of the lungs" is illogical and probably contraindicated.

Adrenalectomy affects not only circulating corticosteroid levels, but also the adrenal medullary hormones. Removal of the adrenal medulla delays the onset of pulmonary oxygen toxicity at hyperbaric pressures.

There is now considerable evidence from many species exposed to hyperbaric oxygen that toxicity is associated with an increase in sympahtoadrenal medullary activity. In animals, sympathomimetic agents augment the onset of pulmonary damage, while sympatholytic agents delay the rate of development of toxicity. Evidence for this is reviewed by Bean and Clark and Lamberts.

There is considerably less information about the importance of the sympahtoadrenal system in the development of pulmonary oxygen toxicity at ambient pressures. Although exogenous epinephrine has been shown to augment the rate of onset of pulmonary oxygen toxicity in rats breathing oxygen at 1 atm, it is known that epinephrine toxicity by itself is associated with pulmonary edema.

From the evidence available, it appears that the neuroendocrine system plays a role of greater importance in the response to hyperbaric than normobaric oxygen, but it is certainly operant in both situations. Bean has suggested that the variation in neuroendocrine activity may account for the "wide variation in the susceptibility and unpredictability of reactions to oxygen at high pressure." This aspect of pulmonary oxygen toxicity is poorly understood and of potentially direct therapeutic importance. At present, data describing protective manipulations in experimental animals are insufficiently understood to permit application to patients at risk from oxygen toxicity.

Discussion and Clinical Recommendations

This review has dealt primarily with the pulmonary manifestations of oxygen toxicity. We acknowledge that this is a limited viewpoint, paying scant attention to the fact that oxygen, at various pressures, affects many, if not all, organ systems. Pulmonary toxicity is essentially the only major manifestation of oxygen overdosage which is observed in clinical practice, with two exceptions: retrolental fibroplasia in neonates, and hyperventilation in patients with chronic hypoxemia and hypercarbia. The other major form of oxygen toxicity has been mentioned briefly. Central nervous system oxygen toxicity, consisting of grand mal seizures, is a matter of concern only in unusual environments in which oxygen at pressures greater than 2.5 atm is inspired. This occurs only in the treatment of certain uncommon diseases in hyperbaric chambers or in deep-sea diving or caisson work. It should be remembered, however, that central neuroendocrine changes may markedly alter the time course and rate of progression of the pulmonary responses to oxygen at exposure levels far below those which produce frank seizure activity. Thus, interrelationships between pulmonary toxicity and neuroendocrine involvement remain an important area of investigation.

That high concentrations of oxygen administered for long periods cause pulmonary toxicity is well documented. Yet it is well to keep in
mind the relative dangers of hypoxia and hypoxia. Only in the past decade has the pathophysiology of hypoxia in the critically-ill patient been commonly understood, and appropriate therapeutic manipulations become normal medical practice. In the course of the development of these treatment techniques, oxygen has been both used and abused, and there is little disagreement that oxygen toxicity is a real iatrogenic disease. This understanding should prove valuable in protecting patients from inappropriate use, but an overreaction to the dangers associated with oxygen supplementation has led to hazardous and poorly-informed assertions. That patients should be exposed to dangerous levels of hypoxia for fear of developing oxygen toxicity is a form of therapeutic nihilism which is obviously self-defeating. It is well to remember that hypoxia is common and that the damage it causes is rapid. Pulmonary injury from oxygen is uncommon and its development is relatively slow. The time-pressure tolerance curves delineating the onset of oxygen damage, discussed above, should provide guidelines for safety in the use of oxygen. In summary:
1) There is currently no evidence that pulmonary oxygen toxicity develops in man at inspired tensions below 0.4-0.5 atm, even with prolonged exposures.
2) No data support the contention that significant toxicity develops in man breathing pure oxygen for 24 hours or less.
3) There is no clinical or experimental information to indicate that patients with pre-existing pulmonary diseases are more sensitive to oxygen toxicity than are normal volunteers.

Therefore, if the discussion is limited to oxygen toxicity of the lung, and not to patients suffering from chronic hypercarbia or other unassociated conditions, several conclusions can be drawn. Oxygen, when administered at atmospheric pressure or less, causes damage only after prolonged exposure. Therefore, oxygen toxicity should not be a consideration intraoperatively, or in resuscitation or transport situations. There is no known contraindication to the use of pure oxygen for brief periods or in emergency situations. However, the rate of development of oxygen damage is a function of both the inspired tension and the duration of exposure. Therefore, it is appropriate to lower oxygen tension as it proves feasible, but only by objective criteria.

The most common setting in which oxygen toxicity becomes a significant clinical problem is in the treatment of severe and prolonged respiratory failure with gross alterations in the efficiency of gas transport across the lung. In such situations, the fraction of the cardiac output which functionally bypasses the lung or incompletely equilibrates with alveolar gas may be high enough that toxic inspired concentrations of oxygen are necessary to maintain viable arterial levels. In such situations, sufficient oxygen must be administered, but manipulations other than an increase in inspiratory tension become increasingly important. Where respiratory failure is sufficiently severe to necessitate the use of toxic concentrations of oxygen, the wide range of therapeutic maneuvers which may partially reverse the pathophysiology seen can make the difference between success and failure. A clear understanding of the disease process and application of available therapeutic measures may serve to reduce shunt fraction and the A-aDO₂ such that less hazardous inspired pressures may be employed. Optimal ventilatory patterns, fluid restriction, maintenance of electrolyte balance, and the institution of positive end-expiratory pressure in the ventilatory cycle are all measures that may serve to increase arterial oxygen tension at a given inspired concentration. The importance of such maneuvers may be illustrated by the following example and by figure 7.

It is important to realize that the increase in arterial oxygen tension for a given alveolar tension decreases markedly as the shunt fraction increases. For high shunt fractions, therefore, there is very little increase in systemic oxygenation as FIO₂ increases. In such a situation, increasing inspired oxygen may have little benefit, and the risk of toxicity will become greater. On the other hand, even small reductions in shunt fraction by maneuvers such as those mentioned above will accomplish far more in removing the patient from the thin line between hypoxia and oxygen toxicity. If a patient has a shunt fraction (Qs/Qt) of 0.4, alteration of FIO₂ will have little effect. We shall assume an arterial-to-venous oxygen content difference of 6 vol per cent, pHa 7.40, PAO₂ 40 mm Hg, and a normal hemoglobin dissociation curve. An FIO₂ of 80 per cent in this patient will yield a Pao₂ of 55 mm Hg. If such a level is not considered adequate and FIO₂ is increased to 100 per cent, the resultant Pao₂ will increase only to 60 mm Hg. Thus, the improvement in systemic oxygenation is extremely small at such high shunt fractions, and at a considerable cost in the rate of development of pulmonary toxicity. If, on the other hand, the shunt fraction were lowered by only 5 per cent under similar conditions, and 80 per cent O₂ were administered, Pao₂ would increase to 65 mm Hg. Thus, although FIO₂ is an important determinant of arterial tension, it is not the only one, and it is important to know when other manipulations may prove decisive.

The avoidance of excessively high oxygen concentrations in inspired gas is a common issue in critical care units, but there is little agreement about criteria for systemic levels which need to be maintained. As has been suggested, in certain circumstances man can survive very low oxygen levels for long periods, but such information cannot readily be
THE TOXICITY OF OXYGEN

extrapolated to the clinical situation. The time necessary for functional acclimatization to altitude is usually not available in acute respiratory failure. In addition, patients frequently have single or multiple system organ failures which may impose oxygenation requirements very different from the normal situation. On the other hand, the maintenance of higher than “normal” arterial oxygen tensions may be quite unnecessary and impose an unwarranted risk of oxygen damage if the concentration needed is high. The level to which the oxygen tension can safely be lowered must remain a clinical judgment in each circumstance. Certain common considerations may be discussed, however. Of the major organs, brain and myocardium have the highest oxygen extraction rates, and thus limit the degree to which oxygenation can be depressed. Nunn suggests that unconsciousness occurs when cerebral venous $P_{O_2}$'s reach 20 mm Hg, which, extrapolated to a healthy individual, would necessitate an arterial oxygen tension of 36 mm Hg. That this level would not be tolerated by most ill patients is clear, and emphasizes Nunn's subsequent point that the calculation quoted is influenced by a host of intervening factors. Clearly, any observable alteration in a critically ill patient which can be ascribed to oxygen deprivation is an indication for increase in oxygen delivery, although not necessarily for an increase in the inspired oxygen concentration. Such manifestations include clouding of the sensorium, cardiac arrhythmias, and decreased renal function. In the therapy of such patients, manipulation of many other factors along the oxygen-delivery chain should be considered. The mere correction of hypoxia by increasing inspired concentrations is an excessively simplistic approach. In any consideration of the acceptable minimum for oxygen levels, consideration must be given to the fact that on-line oxygen-measurement capability is not yet a clinical reality, and an appropriate margin of safety must be allowed. This is particularly important in situations which are in flux or in those instances in which it can be predicted that deterioration of oxygenation will take place. Finally, the degree of sophistication of the intensive care facility, including the nursing staff, will also contribute to determination of the margin of safety which should be allowed in oxygenation.

The treatment of acute respiratory failure is largely quantitative. Therapy is based on titration rather than prescription, and assessment of both dysfunction and therapy is based on measurement as much as or more than on clinical experience. The reality of oxygen toxicity is one of the factors necessitating quantification. Despite extensive research on the subject, the pulmonary toxicity of oxygen is still a potentially lethal phenomenon which limits the salvageability of patients in severe respiratory failure. Experimental observations indicate that the severity of oxygen damage can be attenuated by many manipulations, but no practical measure for influencing the rate of oxygen damage exists, except avoidance of dangerous levels. The ubiquity of the tissue responses to oxygen and the immediate implications for patient care make further research in this field both challenging and of great potential importance.

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236

P. M. WINTER AND G. SMITH

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