The uses of high concentrations of therapeutic oxygen have expanded in recent decades. This situation came about both from the introduction of ventilation by intubation in the Intensive Care setting and with the use of hyperbaric oxygen for the treatment of anaerobic infections. Furthermore, high concentrations of oxygen have been used in deep sea diving and in aviation and space exploration. With potential side-effects of exposure to high concentrations of oxygen it has become increasingly important to understand better the parameters of exposure that produce toxicity, the mechanisms by which it occurs and the potential protective devices against its tissue-damaging effects. It is the purpose of this review to address these considerations. The reader is also referred to other reviews (Clark and Lambertsen, 1971; Mustafa and Tierney, 1978; Deneke and Fanburg, 1980a; Fisher, 1980; Frank and Massaro, 1980) where certain aspects of the subject may be covered in more detail.

Damage to tissues by oxygen seems to be related more to the partial pressure of oxygen than to its percent concentration. Hence, a high concentration of oxygen may be less damaging at high altitude where the atmospheric pressure is reduced than it is for the same concentration at normobaric pressure. The primary target of injury for normobaric hyperoxia is the lung, probably at least in part because lung cells are exposed to higher partial pressures of oxygen than are other cells of the body. With hyperbaric hyperoxia, the rapid onset of convulsions indicates that the central nervous system shows the earliest signs of toxicity. Hence, with higher partial pressures of oxygen than can be achieved under normobaric conditions, tissues of the central nervous system seem to be "more sensitive" than do cells of the lung. It is likely that certain cells of the body, even within the same organ, are more sensitive than others to hyperoxia.

Concentrations (or partial pressures) of oxygen that cause toxicity to living tissues are variable. Plants, at least at stages of mature growth, seem to be more resistant than animals to hyperoxia (Matkovics, 1977). Similarly, aerobic bacteria are more resistant to hyperoxia than are anaerobic ones (McCord, Keele and Fridovich, 1971). In the animal kingdom there is a wide variety of susceptibility to hyperoxia. For example, amphibians may survive indefinitely when exposed to 100% oxygen at atmospheric pressures, while the rat or mouse succumbs within 3-4 days after exposure to the same concentration of oxygen (Clark and Lambertsen, 1971).

The precise concentration of oxygen that is toxic to man has, for obvious reasons, been difficult to establish and probably varies according to age, nutritional status, endocrinological status and the history of previous exposures to oxidants or other substances that may alter mechanisms protective against oxygen toxicity. Some data bearing on physiological and pathological alterations in man exposed to hyperoxia are noted in table I. Needless to say, these data are not precise and provide only guidelines for predicting oxygen toxicity in man exposed to hyperoxia. Although Van De Water and his associates (1970) were unable to find physiological, radiological, or symptomatic alterations in normal subjects exposed to 100% oxygen for 6-12 h, Sackner and associates (1975) have reported the occurrence of tracheitis and decreased velocity of tracheal clearance of mucus in normal men exposed to 90-95% oxygen for 6-12 h. Comroe and others (1945) reported a decreased vital capacity for persons exposed to 100% oxygen for 25 h at sea level. Several physiological alterations, including increased wasted ventilation, increased arteriovenous shunting, decreased static and dynamic compliance and decreased diffusing capacity, have been reported to occur in man exposed to hyperoxia for 24-48 h.

It seems reasonable to conclude from these studies that individuals exposed to 100% oxygen at
normobaric pressures are very likely to incur damage to the lung produced by hyperoxia. The damaging effect may be reversible if exposure to hyperoxia is discontinued after 24–48 h. With more prolonged exposure, more pronounced and possibly irreversible changes occur and the damaging effects may be lethal within a few days. Similar damaging effects of hyperoxia are likely to occur, albeit at a slower rate, for concentrations of oxygen less than 100%. The “safe” concentration of oxygen for humans has not been adequately established, but for practical purposes currently it might be considered that there is a high likelihood of some significant form of oxygen toxicity to the lung at concentrations of oxygen greater than 60–70% at atmospheric pressure.

Whether or not values of hyperoxia less than 60–70%, when given for sufficiently long periods of time, may cause some degree of tissue injury is not known. Data concerning damage by smaller concentrations of oxygen would, of course, be very useful since it is these concentrations of oxygen that are used more frequently in the Intensive Care setting. Although data relating to effects of these lower concentrations of oxygen have been obtained in animal studies (Frank, 1981c; Hayatdavoudi et al., 1981), their direct applicability to human subjects is uncertain. Furthermore, there may be sufficient variability according to factors such as age, nutrition, endocrine status and previous exposures to oxidants, to cause the whole question to be extremely complex when projections are made for an individual patient. Therefore, rather than try to establish precise concentrations of oxygen that produce toxicity, it may be more productive to optimize conditions that protect against oxygen toxicity and to use only a concentration of oxygen necessary to achieve an “adequate” arterial \( P_{\text{O}_2} \) in the clinical setting.

### BIOCHEMICAL REACTIONS INVOLVED IN OXYGEN TOXICITY

According to the free radical theory of oxygen toxicity, the agent responsible for cellular damage is not the \( \text{O}_2 \) molecule, but rather any of a number of oxygen radicals or peroxides generated intracellularly by accelerated metabolic processes during exposure to hyperoxia (Deneke and Fanburg, 1980a; Frank and Massaro, 1980). Metabolic reduction of oxygen can produce these toxic agents (table II).

### TABLE I Normobaric oxygen toxicity in man

<table>
<thead>
<tr>
<th>Duration of exposure to 100% ( \text{O}_2 ) (h)</th>
<th>Changes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–12</td>
<td>No changes in ( (P_{\text{AO}<em>2} - P</em>{\text{PA}_2}) ), PA pressure, pulmonary resistance, cardiac output or pulmonary extravascular water</td>
<td>Van De Water and others (1970)</td>
</tr>
<tr>
<td>21–44</td>
<td>No detectable physiological alterations</td>
<td>Singer and others (1970)</td>
</tr>
<tr>
<td>40</td>
<td>↑ Wasted ventilation and A-V shunting</td>
<td>Barber, Lee and Hamilton (1970)</td>
</tr>
<tr>
<td>25</td>
<td>↓ Vital capacity</td>
<td>Comroe and others (1945)</td>
</tr>
<tr>
<td>30–48</td>
<td>Small change in static and dynamic compliance and in diffusing capacity</td>
<td>Caldwell and others (1966)</td>
</tr>
</tbody>
</table>

### BIOCHEMICAL REACTIONS INVOLVED IN OXYGEN TOXICITY

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Major sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>( O_2 + e^- \rightarrow O_2^- ) (superoxide)</td>
<td>Phagocytic cells, Mono-oxygenases, Xanthine oxidase reaction</td>
</tr>
<tr>
<td>( O_2 + 2e^- + 2H^+ \rightarrow H_2O_2 ) (hydrogen peroxide)</td>
<td>Xanthine oxidase reaction, ( O_2^- ) dismutation</td>
</tr>
<tr>
<td>( O_2 + 3e^- + 3H^+ \rightarrow H_2O + OH^- ) (hydroxyl radical)</td>
<td>Fenton reaction</td>
</tr>
<tr>
<td>( O_2 + 4e^- + 4H^+ \rightarrow 2H_2O ) (water)</td>
<td>Cytochrome oxidase reaction</td>
</tr>
</tbody>
</table>
Superoxide radical ($O_2^-$) is generated as part of the bactericidal function of phagocytes (Babior, Kipnes and Curnutte, 1973; Hoffman and Autor, 1980), as a result of microsomal oxidation reactions (Aust, Roerig and Pederson, 1972; Hirata and Hayaishi, 1977) and in many autoxidations of biological materials (Misra and Fridovich, 1972; Misra, 1974; Sligar et al., 1974). Superoxide may participate in some cellular oxidations (Bors, Saran and Czapski, 1980; Fee, 1980). It may also contribute to the formation of at least two other toxic oxidant species (Fridovich, 1978; Halliwell et al., 1980). $O_2^-$ spontaneously dismutes to hydrogen peroxide ($H_2O_2$) in acid or neutral solution by the following reactions:

$$2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$$

(Halliwell, 1978; McCord and Day, 1978). Both $H_2O_2$ and $OH^-$ have demonstrated biological activity (McCord and Fridovich, 1978). $OH^-$ is very reactive and would not be able to diffuse far from the site of generation without reacting with some biological molecule. $H_2O_2$, which is less reactive, could diffuse through solutions or membranes to cause damage at small distances from its origin. The question of which oxygen radical species is responsible for a given type of oxygen damage is complicated by the fact that many of the primary reactions of $H_2O_2$ or $OH^-$ result in the formation of cellular peroxides or free radical species. Peroxides also decompose to form other radicals in vivo. The net result is a cascade chain reaction which generally results in a complex mixture of oxidized products, making the analysis of initial events complex.

The types of damage caused by oxygen radicals include lipid peroxidation, oxidation of protein sulphhydryls and oxidation of nucleic acids (Borg et al., 1978; Fridovich, 1978). Thus, oxygen radicals can cause membrane damage, enzymic inactivation and genetic damage, and cell death may result from a wide variety of cellular injuries.

Natural defence mechanisms are designed to cope (presumably adequately) with radicals produced by normal oxygen tensions, although it has been speculated that various manifestations of ageing are results of chronic exposure to oxygen at normal tensions. At increased oxygen concentrations natural defences are overwhelmed, resulting in excess radical-related cell damage. When the rate of this damage exceeds the rate of repair, cell and organism death results.

Various compounds that act as free radical quenchers or antioxidants and several enzyme systems have been identified as protective against oxygen radicals and their resulting damage. Of primary importance is reduced glutathione (GSH), which is a preferential substrate for many oxidizing agents, thus sparing protein SH groups from oxidation (Kosower, 1976). GSH is also a substrate for glutathione peroxidase which converts $H_2O_2$ or lipid peroxides to water or non-toxic lipid hydroxides (Flohé, Gunzler and Ladenstein, 1976). The oxidized glutathione (GSSG) is reduced by glutathione reductase. The source of reducing activity is NADPH generated by the oxidation of glucose-6-phosphate in the hexose monophosphate shunt metabolic pathway. These reactions are shown in figure 1.

Other cellular enzymes protective against free radicals produced by hyperoxia include superoxide dismutase (SOD) and catalase (Fridovich, 1978; McCord and Fridovich, 1978). Various types of SOD are found in nature. These differ both in structure and in the metal ligand in the active site. Bacterial SOD are iron or manganese enzymes. The mitochondria of eucaryotic cells have a manganese SOD similar to that of bacteria. Cytoplasmic SOD is a copper–zinc enzyme. Until recently it was presumed that all organisms that reduced oxygen contained SOD, but various species of mycoplasma

![Figure 1. Cellular enzyme systems protective against oxygen radicals.](https://academic.oup.com/bja/article-abstract/54/7/737/308135)
have now been shown to carry out aerobic metabolism without protection from endogenous SOD (Lynch and Cole, 1980). Nevertheless, SOD undeniably has a major role in oxygen defences (Fridovich, 1978). SOD catalyses the reaction $2\text{O}_2^+ + 2\text{H}^+ \rightarrow \text{H}_2\text{O}_2 + \text{O}_2$. Catalase catalyses the reaction $2\text{H}_2\text{O}_2 \rightarrow 2\text{H}_2\text{O} + \text{O}_2$. Other cellular compounds identified as antioxidants and radical quenchers include ascorbic acid (vitamin C), cysteine and $\alpha$-tocopherol (vitamin E). Biochemical studies of oxygen toxicity have tended to focus on changes in various compounds and enzymes noted above to identify reasons for increased or decreased susceptibility to oxygen.

Lungs contain copper–zinc and manganese SOD, catalase, glutathione peroxidase, glutathione reductase, and glucose-6-phosphate dehydrogenase (Crapo and Tierney, 1974; Kimball et al., 1976). The amounts of these enzymes vary widely with species and age (Yam, Frank and Roberts, 1978). There is no apparent correlation between the absolute amounts of these enzymes and oxygen resistance among the various groups of animals studied. However, changes in concentrations of these enzymes within an animal are related to the development of tolerance to hyperoxia. This will be discussed further below.

**LUNG PATHOLOGY RESULTING FROM EXPOSURE TO HYPEROXIA**

There seems to be a variability in the sensitivity of various cell types of the lung to toxic treatments such as hyperoxia. The particular cell type injured early in the process of toxicity may determine the chain of pathological events and the accompanying physiological alterations that follow exposure to hyperoxia. Attempts have been made to unravel the pathogenesis of cellular injury occurring as a result of exposure to hyperoxia. Although there is some evidence that alveolar cells may be injured by hyperoxia (Obara, Sekimoto and Iwai, 1979; Sackner, 1979), it appears that the primary pathological event is injury to the alveolar–capillary unit (Bowden and Adamson, 1974; Weibel, 1971). With careful longitudinal studies in animals, it appears that the endothelial cell and the Type II alveolar cell are the earliest sites of injury (Crapo et al., 1978, 1980) and injury to these cells may lead to sequential lung damage as a result of loss of integrity of the barrier between the alveolus and the capillary.

At concentrations of 95–100% oxygen this damage is severe, resulting in a major loss of endothelium with accompanying oedema and subsequent death (Crapo et al., 1980). After prolonged exposure of animals to sub lethal hyperoxia (60–85% oxygen), there are numerous non-specific pathological findings including the presence of atelectasis, oedema, alveolar haemorrhage, inflammation, fibrin deposition and thickening and hyalinization of alveolar membranes (Crapo et al., 1980; Chvapil and Peng, 1975).

The role of secondary cellular infiltration, such as that of leucocytes, in the pathogenesis of oxygen toxicity is uncertain. It has been postulated that leucocytes may be important in formation of free oxygen radicals that cause injury to the lung. Although it is well known from isolated cell studies that oxygen is quite toxic to lung cells in the absence of leucocytes, the leucocyte contribution may be important in producing the acute stages of oedema leading to death (Fox, Shasby et al., 1981).

With discontinuation of exposure to hyperoxia, at least two events may potentially develop as a result of the exposure. The first of these is the proliferation of the Type II alveolar cell that appears to constitute a restructuring of the alveoli of the lung (Crapo et al., 1978) and the second is a fibroblastic proliferation that may lead to interstitial fibrosis (Chvapil and Peng, 1975). The first event seems to be reparative in nature and may have the potential to produce a functional alveolar unit. Of course, capillary regeneration would also be required and little is known about this process. The production of fibrosis does not seem to have any utility in recovery and may be simply a manifestation of the aberrant proliferation of a cell type (the fibroblast) that is relatively insensitive to hyperoxia. Histological evidence of the tissue changes of injury and recovery may overlap one another.

**Proliferation of the endothelium occurs in rats exposed to sub lethal concentrations of oxygen (Crapo et al., 1978, 1980). Whether or not structural alterations such as this play a significant role in subsequent protection against hyperoxia is not known.**

**In vitro model systems**

Work done over the past several years using lung cells in culture has confirmed that individual cells exposed to hyperoxia can be killed without interactions with other cells. This has been most extensively demonstrated for endothelial cells and alveolar macrophages. Both macrophage phagocytic function and chemotaxis are damaged by values of hyperoxia as small as 40–60% (Simon, Axline and Robin, 1978; Raffin et al., 1980; Wolff et al., 1978;
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Bowles, Dauber and Daniele, 1979). Endothelial cells derived from aorta or calf pulmonary arteries show evidence of impaired uptake of serotonin or \( \alpha \)-aminoisobutyric acid by 24–72 h of exposure to 80–95% oxygen (Block and Stalcup, 1981; S. L. Lee and colleagues, unpublished data). Endothelial cells have also been shown to be damaged by morphological criteria within 24 h after exposure to 80% oxygen (Lee at al., 1982).

In addition to cell cultures, organ cultures and lung explants have been used to model the effects of oxygen on the lung. Cessation of ciliary activity has been shown in organ cultures of tracheal epithelium after 2–6 days of exposure to 60–80% oxygen (Boat, 1979).

Damage by hyperoxia has recently been reported in explants of parenchymal tissues from rat and rabbit lung (Boat, 1979; Martin et al., 1981). Release of a chromium-51 indicator from labelled lung tissue in culture showed that significant cell damage occurred within 18 h of exposure to 95% oxygen. The effects were prevented by SOD, catalase, ascorbate and \( \alpha \)-tocopherol for the rat tissue and by catalase and \( \alpha \)-tocopherol for the rabbit tissue.

A third in vitro model, the perfused lung, has proved to be a sensitive model to detect early functional damage to the pulmonary endothelium. Hyperoxia has been shown to impair the ability of the perfused lung to remove various compounds, including 5-hydroxytryptamine and prostaglandins, from the pulmonary circulation (Block and Fisher, 1977; Klein et al., 1978).

These in vitro systems have demonstrated that hyperoxia causes damage to individual lung cell types and to isolated lung tissues that is independent of any influx of cells from the circulation. However, oxygen radical production by activated PMN recruited to the lung during exposure to oxygen may be a significant factor in the resulting lung damage and death. Superoxide and hydrogen peroxide generated by PMN have been shown to cause damage to isolated endothelial cells in vitro (Sacks et al., 1978; Weiss et al., 1981). More recently, Repine and co-workers (Fox, Hoidal et al., 1981; Shasby et al., 1981; Harada et al., 1982) have reported: (a) correlations between PMN recruitment and lung damage in both rats and rabbits, (b) protection against hyperoxia death in rabbits by nitrogen mustard-induced neutropenia, and (c) the production of PMN chemotactic factors by oxygen-exposed rabbit macrophages which may be responsible for the influx of PMN into the lung. These data support a role for leucocyte \( \mathrm{O}_2^\cdot \) in hyperoxic lung damage.

It has also been reported that SOD administered by constant infusion provides partial protection against oxygen damage in the lung (McLennan and Autor, 1978). This SOD would be expected to be most effective against extracellular superoxide sources such as that generated by activated leucocytes.

Involvement of oxygen radicals

A central question in confirming the oxygen radical mechanism proposed for oxygen toxicity is whether hyperoxia does indeed increase intracellular oxygen radical production. Freeman and co-workers have reported increases in \( \mathrm{O}_2^- \) production with increased exposure to oxygen in mitochondrial and microsomal fractions of rat lungs (Freeman and Crapo, 1981; Brown, Freeman and Crapo, 1981). Although increases in \( \mathrm{O}_2^- \) and other oxygen radicals have resisted measurement in intact cells and tissues, much indirect evidence exists that these radicals are indeed responsible for hyperoxic damage to cells. Enzymically-generated oxygen radicals have been shown to mimic hyperoxic damage to isolated cells as well as to perfused lung (Fox and Autor, 1978; Steinberg et al., 1979; Johnson et al., 1981; Tate et al., 1981). Also, inhibitors of oxygen radicals such as superoxide dismutase or thiourea and dimethylthiourea (OH' quencher) have been shown to protect isolated cells, organ cultures and perfused lungs from oxygen damage (Block and Fisher, 1977; McLennan and Autor, 1978; Tate et al., 1981).

Summary of events leading to hyperoxic death

At the current time the chain of events leading to hyperoxia-induced death can be best summarized as shown in figure 2.

The relative importance of pathways a and b in figure 2 may depend on oxygen concentration, species or age, but it is likely that both internal and PMN-generated oxygen radicals contribute to the ultimate death of the animals.

MECHANISMS OF DEVELOPMENT OF TOLERANCE TO HYPEROXIA

General

The ability to develop tolerance to oxygen exposures varies widely among animals (Clark and Lambersten, 1971). Age and species affect both initial resistance to hyperoxia and the ability to increase resistance after various stimuli. Reasons for the
innate tolerance to oxygen of such animals as turtles, frogs and chickens are unknown but may be correlated with metabolic rate (Barthelemy, Belaud and Chastel, 1981). However, some mechanisms for variation in oxygen resistance in animals of different ages and for the differences in ability to develop tolerance have been at least partially explained.

**Age**

The young of many species are able to become tolerant to 100% oxygen rapidly enough to prevent death, even if the adult animals are killed by oxygen (Frank, Bucher and Roberts, 1978). The ability of these young animals to resist oxygen toxicity appears to be correlated with their ability to increase concentrations of protective enzymes in response to exposure to oxygen rapidly enough to prevent death (Frank, Bucher and Roberts, 1978; Bucher and Roberts, 1981). Various investigators have reported that significant increases, within 24–48 h, in concentrations of SOD, glucose-6-phosphate dehydrogenase, glutathione peroxidase and reductase, and in some cases of catalase, enable these animals to resist 100% oxygen. The observation appears to be species-specific since young rabbits, mice and rats show this response, while guineapigs and hamsters do not. Young guineapigs and hamsters, which are killed by 100% oxygen, cannot increase these enzymes soon enough to provide protection.

**Pre-treatment**

Adult small animals cannot react to 100% oxygen exposure rapidly enough to survive. However, the rat is capable of responding to 80–85% oxygen by increasing concentrations of SOD and the glutathione-related protective enzymes within 3–5 days of exposure (Crapo and Tierney, 1974; Kimball et al., 1976; Tierney, Yang and Ayers, 1975). The animals pre-exposed to a sublethal concentration of oxygen are able to tolerate prolonged exposures to 100% oxygen. Lung damage does occur, but the effects are not lethal in most cases. Unfortunately, toxic concentrations of oxygen are required for both increases in protective enzymes

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**Fig 2.** Chain of events currently believed to lead to hyperoxia-induced death.
and the development of tolerance. Frank (1981c) has reported that pre-exposure of rats to 40–60% oxygen does not increase either protective enzyme concentrations or tolerance to subsequent exposure to 100% oxygen. In fact, these pre-exposures appear to increase the rate of damage caused by 100% oxygen, indicating that the lungs were already partially damaged by the exposure to lower concentrations of oxygen.

Other treatments that increase concentrations of protective enzymes in rats have also been found to increase tolerance to hyperoxia. These treatments will be discussed in detail in the next section. Thus, the common mechanism for development of tolerance to hyperoxia in adult rats, as well as in various neonatal animals, appears to be the stimulation of the production of the protective enzymes.

**Cellular adaptation**

Attempts have been made to determine which lung cell types are responsible for the induction of enzymes and the development of tolerance to hyperoxia. The most definitive studies have been on the lung macrophage. Various investigators have shown that adult rat lung macrophages exposed to oxygen in tissue culture or in vivo do not increase concentrations of SOD (Stevens and Autor, 1977; Deneke, Bernstein and Fanburg, 1978). Macrophages of infant rats, however, have been shown to increase mitochondrial SOD in response to exposure to hyperoxia in vivo or in vitro (Stevens and Autor, 1977; Autor and Stevens, 1980). Induction of SOD in cultured lung macrophages of adult mice has been reported as well as in macrophages isolated from guineapigs exposed to oxygen in vivo (Simon et al., 1977; Rister and Baehner, 1976). Thus, although there are instances of induction of SOD in adult lung macrophages, the induction does not correlate well with either induction of total lung SOD or with survival in hyperoxia.

More recently, Forman and Fisher (1981) have reported increases in mitochondrial SOD in lung Type II pneumocytes from rats exposed to oxygen in vivo, but not in cells exposed to hyperoxia in vitro. No changes were observed in other protective enzymes of these cells. Freeman, Mason and Crapo (1981), however, reported increases in several antioxidant enzyme concentrations in Type II cells isolated from lungs of rats exposed to oxygen. Confluent endothelial cells from pig pulmonary artery and aorta increase concentrations of SOD in response to hyperoxia (Ody et al., 1980). Many of the results obtained with cells in culture appear to be related to the source of the cells and to culture conditions, making it difficult at present clearly to relate these observed changes to mechanisms of adaptation of the lung to hyperoxia (Housset and Junod, 1981).

**FACTORS INFLUENCING TOLERANCE TO HYPEROXIA**

**General**

Several constitutional and environmental factors may influence tolerance to hyperoxia. Some factors which increase or decrease tolerance have rationales for their effects related to the biochemical mechanisms noted previously. Among factors best explored experimentally are metabolic alterations, diet, administered medications and chemicals and prior inhalation of oxygen itself. It is likely that the number of these factors will increase, but our current knowledge of them is discussed below.

**Metabolic factors**

If the cause of hyperoxic damage is primarily oxygen radicals generated intracellularly by metabolic processes, factors that decrease metabolism, such as hypothyroid, hypothermic or hypopituitary states, might be expected to provide protection against hyperoxia.

Hypophysectomized rats have been reported to be more resistant to oxygen toxicity than normal controls (Bean and Smith, 1952). Hypothermia decreased retinal damage, but not lung damage, produced by hyperoxia in mice (Hellstrom and Nergardh, 1965). The rate of oxygen-induced rat lung damage has been reported to be a function of the temperature of the exposure chamber (McLennan and Autor, 1979). Hypothyroidism decreases oxygen utilization (Galton, 1978) and administration of thyroid hormone has been reported to increase oxygen toxicity in rats (Clark and Lambertsen, 1971).

**Administered medications and chemicals**

Various drugs increase the rate of production of oxygen radicals (Hassan and Fridovich, 1979). Many of these drugs react by disrupting mitochondrial oxidative phosphorylation so as to result in increased production of $O_2^-$. Other drugs such as nitrofurantoin cause an increase in $O_2^-$ or $OH^-$ production as part of their metabolism (Boyd et al., 1977). Some of these agents are indicated in
Many of these compounds have been found to increase the production of free radicals in mammalian cells in vitro or in bacteria, but only a few have been directly implicated in the increase in toxicity in animals or humans. Paraquat is the most widely investigated of these compounds (Fisher, Clements and Wright, 1973; Autor, 1974). There is some evidence that the lethal effect of Paraquat is not directly caused by free radical production, but rather by the resultant depletion of cellular NADPH (Forman, Nelson and Fisher, 1980).

Various drug treatments may also interfere with mechanisms protective against hyperoxia (Yam and Roberts, 1979). An often noted compound is diethyldithiocarbamate (DDC) that chelates copper and inhibits SOD (Frank, Wood and Roberts, 1978). Disulfiram (Antabuse) is metabolized to DDC. Disulfiram also reacts directly with protein sulphydryls, thereby inhibiting a wide variety of enzymes (Niems, Coffey and Hellerman, 1966). The exact mechanism by which disulfiram potentiates oxygen toxicity is unknown (Deneke, Bernstein and Fanburg, 1979; Forman, York and Fisher, 1980).

Other agents administered before or concomitant with oxygen exposure have been shown to produce tolerance to hyperoxia in rats. Prior injury with agents such as alphanaphthylthiourea or oleic acid provides protection against hyperoxia (Tierney, Ayers and Kasuyama, 1977). Endotoxin administered concomitantly with or slightly before exposure to hyperoxia also protects against toxicity by hyperoxia (Frank, Yam and Roberts, 1978: Frank, Summerville and Massaro, 1980). A near lethal dose of DDC given concomitantly with exposure to hyperoxia increases survival of rats and is accompanied by increases in glutathione-related enzymes, but not in SOD (Deneke and Fanburg, 1980, b).

The mechanism by which these treatments increase oxygen tolerance and tissue enzyme concentrations is not known, but may involve an early increase in cellular oxygen radical concentration or peroxidation which stimulates an increase in the enzymes rapidly enough to protect the lung. The induction of the protective enzymes by any of these agents has been shown only in adult rats. Adult mice, hamsters, rabbits or guineapigs apparently cannot increase protective enzyme concentrations in response to the agents (Frank, Bucher and Roberts, 1978; Lanir, Kerem and Gershon, 1981). Whether similar responses may occur in humans is not known.

### Table III

<table>
<thead>
<tr>
<th>Potentiation</th>
<th>Protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Hyperthyroidism</td>
<td>(1) Avoidance of potentiators</td>
</tr>
<tr>
<td>(2) Hyperpyrexia</td>
<td>(2) Antioxidants such as ascorbate or α-tocopherol (in deficient patients)</td>
</tr>
<tr>
<td>(3) Dietary deficiency (protein, selenium, copper)</td>
<td>(3) Superoxide dismutase</td>
</tr>
<tr>
<td>(4) Drugs such as disulfiram (Antabuse), nitrofurantoin, ? chemotherapeutic agents</td>
<td>(4) Agent to stimulate protective enzymes such as endotoxin or diethyldithiocarbamate</td>
</tr>
<tr>
<td>(5) Exogenous agents such as Paraquat</td>
<td></td>
</tr>
<tr>
<td>(6) Radiation</td>
<td></td>
</tr>
</tbody>
</table>

### Diet

Deficiencies of several nutrients may decrease tolerance to exposure to hyperoxia. Administration of a diet deficient in protein to rats for 6 days produced an increased susceptibility to hyperoxia (Deneke, Gerhoff and Fanburg, 1981a, b). The increased toxicity was reversed by the addition of cysteine, cystine or methionine to the diet. Rats on unsupplemented low protein diets could not increase concentrations of lung glutathione normally in response to oxygen exposure. It was concluded that the increased toxicity to hyperoxia in the protein-deficient animals was probably a result of the lack of a cysteine precursor necessary for the synthesis of the glutathione tripeptide. Addition of the supplementary amino acid to a normal protein diet did not confer added protection to these animals. Frank (1981a) has also reported increased oxygen sensitivity in undernourished newborn rats.

Deficiencies of vitamins or trace metals in diets have also been found to produce increased susceptibility of the experimental animal to hyperoxia. A deficiency of α-tocopherol produces increased oxygen toxicity, probably as a result of the ability of α-tocopherol to quench free radicals (Tierney, Ayers and Kasuyama, 1977). Similarly, deficiencies of the trace metals, copper or selenium, in the diet produce increased susceptibility to hyperoxia (Cross et al., 1977; Jenkinson, Lawrence and Burke, 1980). Copper is a component of the active site of cytoplasmic SOD and selenium is necessary for the activity of glutathione peroxidase. A diet of saturated fatty acids also appears to increase oxygen sensitivity in rats (Kehrer and Autor, 1978). Unfortunately, dietary supplementation with antioxidants or radical...
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quenchers has not been found to increase survival in non-deficient animals exposed to hyperoxia.

Changes in oxygen concentrations

Hypoxia, altitude acclimatization, sublethal hyperoxia and intermittent lethal hyperoxia have all been shown to stimulate the development of tolerance to hyperoxia in rats. The mechanism in each case seems to be similar. Hypoxia has been shown to increase concentrations of SOD and other protective enzymes (Frank, 1981b). Altitude acclimatization is essentially long-term exposure to hypoxia (Brauer et al., 1970). Sublethal hyperoxia, as stated earlier, stimulates protective enzymes, probably as a result of a response to increased tissue oxygen radicals. Intermittent exposure to 100% oxygen allows time for protective enzyme concentrations to increase before severe toxic effects occur (Hendricks et al., 1977; Paegle, Bernhard and Turndorf, 1977; Frank, 1981c).

CONCLUSIONS

There is little likelihood of the immediate development of a substitute gas for oxygen or improved methods for delivery of oxygen to tissues at lower partial pressures. Therefore, the best current approaches to protection against oxygen toxicity are avoidance of potentiating substances or conditions and the development of protective compounds that are in themselves non-toxic. Although these approaches may be counterproductive in situations such as treatment of anaerobic infections, where the damaging effect of oxygen is needed for therapy, they are very appropriate in the Intensive Care setting where oxygen toxicity is only a byproduct of the treatment.

Methods to prevent potentiation of oxygen toxicity that have some established scientific validity and potential utility are noted in table III. These methods are directed toward the avoidance of circumstances, conditions or accompanying medications that may potentiate oxygen toxicity. It has been established in experimental animal models that factors that increase tissue metabolism, such as hyperpyrexia or hyperthyroidism potentiate oxygen toxicity (Clark and Lambertsen, 1971). Hence, it would seem reasonable to avoid increased body temperatures and to treat hyperthyroidism vigorously in patients who are being subjected to hyperoxia. Similarly, as also indicated previously in this review, certain nutritional alterations may potentiate toxicity resulting from hyperoxia. Despite adequate caloric replacements with carbohydrates, the administration of proteins is frequently reduced in patients in the Intensive Care setting. If animal experimental data can be applied to humans, it would seem appropriate to be certain that patients are receiving adequate intakes of sulphur-containing amino acids (Deneke, Gershoff and Fanburg, 1981a, b).

Avoidance of any substances or therapies that may potentiate oxygen toxicity are similarly important. In this context, it has been demonstrated in animals that disulfiram, a drug used for aversion therapy of alcoholism, potentiates oxygen toxicity. Although it is unlikely that this drug will be used with any regularity in an Intensive Care setting, the observation that it potentiates oxygen toxicity should be a warning that other drugs may produce a similar effect. A more likely drug to be used in the Intensive Care setting is the antibiotic nitrofurantoin. It is now recognized that this drug may produce lung toxicity by increasing oxygen free radical formation (Boyd et al., 1977). Whether or not concentrations of nitrofurantoin or similar drugs that may potentiate oxygen toxicity are ever achieved in humans is unknown, but it is theoretically possible. Chemotherapeutic agents and radiation therapy may have synergistic effects with those produced by hyperoxia, and these possibilities must be kept in mind when planning therapy for a patient in an Intensive Care setting.

It is known that the herbicide, Paraquat, increases superoxide radical production by the respiratory chain and is more toxic in hypoxia than normobaric environments (Fisher, Clements and Wright, 1973). Hence, administration of increased oxygen concentrations to a patient who has arrived in the Intensive Care setting as a result of ingestion of Paraquat may by counterproductive.

It has clearly been shown that the administration of non-lethal hyperoxia to experimental rats results in increased resistance to 100% oxygen by these animals. As noted earlier in this review, this is related to stimulation of enzymes protective against hyperoxia. It has also been shown that this effect is species-specific for the rat, at least in the experimental animal. If the strategy can be applied to the human, it would require graded administration of oxygen to patients. In a practical sense, this probably occurs in the Intensive Care Unit anyway since increase in concentrations of oxygen usually used in therapy are given incrementally because of the usual gradual deterioration of patients. Hence, it is un-
likely that any further benefit will be achieved from use of a strategy that utilizes pre-exposure to non-lethal values of hyperoxia in the Intensive Care setting.

More promising may be the use of other substances that stimulate the formation of enzymes protective against formation of free oxygen radicals. Endotoxin (Frank, Summerville and Massaro, 1980) and diethyldithiocarbamate (Deneke and Fanburg, 1980b) are two such compounds that in combination with oxygen may stimulate enzymes protective against oxygen radicals and thereby induce resistance to tissue damage from these radicals. The use of diethyldithiocarbamate in experimental animals seems to require a dosage that is close to a toxicity value and therefore may not be practical in the Intensive Care setting. Whether or not endotoxin will have applicability to human subjects is not known. Since this compound is known also to produce toxic effects, modifications of it may be required before any testing in human subjects.

Although antioxidants such as ascorbate and α-tocopherol are clearly protective against hyperoxia in the vitamin-deficient animal, there has not yet been any evidence that supplementary doses of these antioxidants would be useful as a protective agent against hyperoxia in an individual who is not vitamin deficient.

The administration of superoxide dismutase would be an obvious protective mechanism against hyperoxic damage. McLennan and Autor (1978) have demonstrated that continuous intra-peritoneal infusion of superoxide dismutase confers some protection against pulmonary oxygen toxicity in the rat. There has been at least one report on the administration of this enzyme in the neonate (Rosenfeld et al., 1980).

REFERENCES


Tolerance and cross-tolerance using NO₂ and O₂ II pulmonary morphology and morphometry. J. Appl. Physiol., 44, 370
— — (1981c). Endotoxin reverses the decreased tolerance of rats to 95% O₂ after pre-exposure to lower O₂. J. Appl. Physiol., 51, 557.


