6 Oxygen Toxicity

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Prolonged exposure to oxygen at high pressure can have toxic effects, particularly on the central nervous system, but at pressures used clinically it does not pose a problem. The main topics discussed here are:

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Introduction

Priestley (1775, see Chapter 1), the discoverer of oxygen, theorized about the effects of hyperoxia in this charming passage:

We may also infer from these experiments, that though pure dephlogisticated air might be very useful as a medicine, it might not be so proper for use in the healthy state of the body: for, as a candle burns out much faster in dephlogisticated than in common air, so we might, as might 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.

Paul Bert (1878, see Chapter 1) was the first to actually document the toxicity of oxygen. He conducted experiments to test the effects of hyperbaric oxygen (HBO), not only on himself but also on other life forms. Indeed, seizures resulting from the toxicity of oxygen to the central nervous system are still referred to as the "Paul Bert effect." Although his work is a classic, Bert completely missed pulmonary toxicity as an effect of normobaric oxygen. This was later discovered by Lorraine Smith (1899) and is fittingly referred to as the "Lorraine Smith effect." Bean (1945) studied the toxic effects of continuous exposure to HBO beyond the point of seizures, to irreversible neurological damage and eventual death; this problem is now widely known as the "John Bean effect."

Behnke *et al* (1936) carried out a variety of experiments in human subjects to show the effects of oxygen toxicity. As a result of these earlier studies it became generally accepted that a 3-h exposure at 3 ATA and a 30- to 40-min exposure at 4 ATA were the limits of safe tolerance by healthy human adults. It is now generally accepted that HBO at 3 ATA affects primarily the nervous system, while the respiratory system is affected independently at 2 ATA. There is a vast amount of literature on basic mechanism of oxygen toxicity (Bean 1945; Balentine 1982).

This chapter describes mainly the toxic effects of HBO. Normobaric hyperoxia, which usually leads to pulmonary oxygen poisoning, has been dealt with in detail elsewhere (Jain 1989a).

Pathophysiology of Oxygen Toxicity

The molecular basis of CNS as well as pulmonary oxygen poisoning, involves generation of reactive oxygen species (ROS). This has been known as the free radical theory of oxygen poisoning. The basis of this theory, for the CNS oxygen toxicity, is that an increased generation of ROS during HBO may ultimately lead to alterations in cerebral energy metabolism and electrical activity due to membranes lipid peroxidation, enzyme inhibition, and/or enzyme modulation. Although HBO-induced generation of ROS could directly alter the functions of various SH-containing enzymes, membrane-bound enzymes and structures as well as the nucleus, the physiological effects of HBO may also indirectly cause hypoxic-ischemia, acidosis, anemia, and hyperbilirubinemia.

At higher pressures of oxygen, events in the brain are a prelude to a distinct lung pathology. The experimental observation that CNS-mediated component of lung injury can be attenuated by selective inhibition of neuronal nitric oxide synthase (nNOS) or by unilateral transection of the vagus nerve has led to the hypothesis that extrapulmonary, neurogenic events predominate in the pathogenesis of acute pulmonary oxygen toxicity in HBO, as nNOS activity drives lung injury by modulating the output of central autonomic pathways (Demchenko *et al* 2007).

Free Radical Mechanisms

Oxygen free radicals are products of normal cellular oxidation- reduction processes. Under conditions of hyperoxia, their production increases markedly. The nature of the ox-

Table 6.1
Animal Experimental Studies of the Effect of HBO on Brain Lipoperoxide Levels

Authors and year	Pressure	Effects
Zirkle *et al* (1965)	4 ATA	Clinical level of CNS toxicity correlated with elevated lipoperoxide content; convulsions were considered to be due to raised AChE (acetylcholinesterase) activity
Galvin (1962)	2 ATA	Cerebral peroxide level not elevated; no difference in the peroxide level between convulsing and nonconvulsing animals
Jerrett *et al* (1973)	5 ATA	H_2O_2 levels were elevated except in those animals given supplemental α-tocopherol
Yusa *et al* (1987)	3 ATA	Rise of H_2O_2 level in brain by 300% when symptoms of CNS toxicity became apparent
Torbati *et al* (1992)	5 ATA	Direct demonstration of reactive oxygen species before onset of CNS convulsions

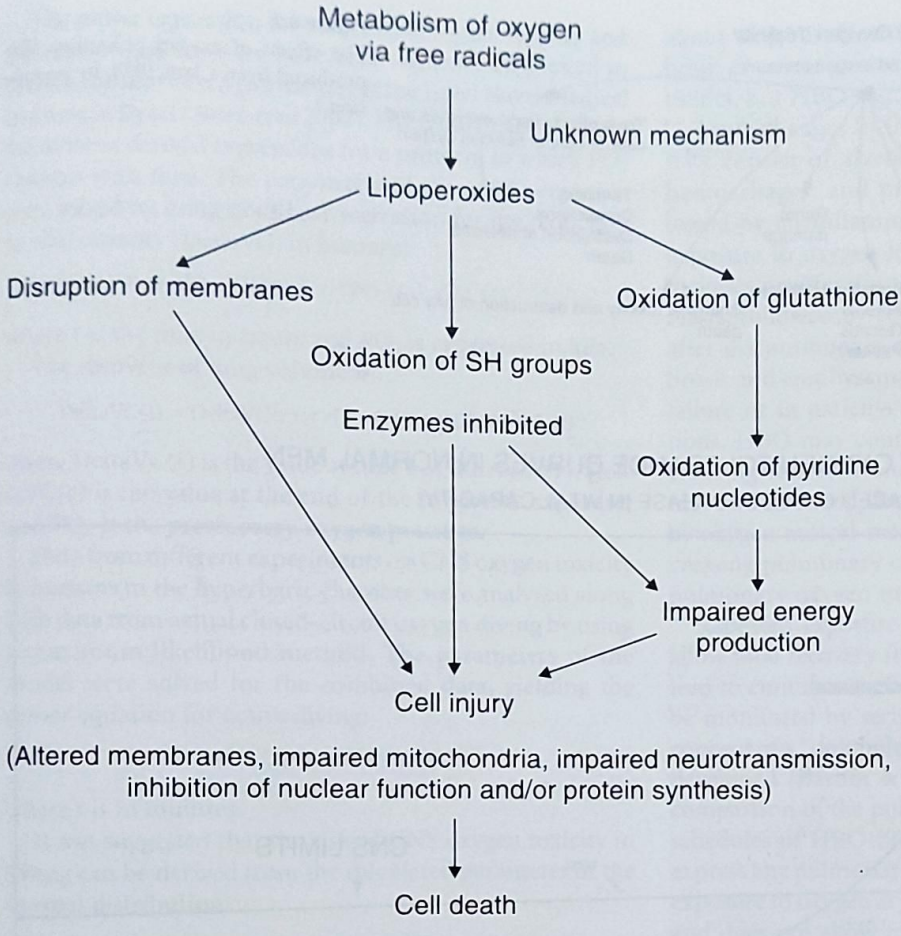

Figure 6.1
Summary of the hypothesis of oxygen toxicity. SH = sulfhydryl. (Reproduced from Chance and Boveris 1978, by permission.)

ygen molecule makes it susceptible to univalent reduction reactions in the cells to form superoxide anion (O_2^-) a highly reactive, cytotoxic free radical. In turn, other reaction products of oxygen metabolism, including hydrogen peroxide (H_2O_2), hydroxyl radicals ($OH\cdot$), and singlet oxygen ($^1O_2$), can be formed. These short-lived forms are capable of oxidizing the sulfhydryl (SH) groups of enzymes, interact with DNA, and promote lipoperoxidation of cellular membranes. Animal studies showing the effect of HBO in raising the cerebral peroxide content and correlating it with CNS toxicity are listed in Table 6.1.

Boveris and Chance presented an excellent unifying concept of the mechanism of oxygen toxicity in 1978, which is a classic now. H_2O_2 generation as a physiological event has been documented in a variety of isolated mitochondria and is rapidly enhanced by hyperoxia. Superoxide ions, generated submitochondrial fractions, are the source of H_2O_2 (Boveris & Chance 1978). This hypothesis is shown in Figure 6.1. As a primary event, the free radical chain reactions produce lipoperoxidation. Lipoperoxides, in turn, will have disruptive effects on the structure of the biomembranes, inhibit enzymes with SH groups, and shift the cellular redox state of glutathione toward oxidation. This will be transmitted through the secondary events to pyridine nucleotides, with the mitochondrial NADH oxidation resulting in impaired energy production. Enzyme inhibition, altered energy production, and decrease or loss of function may be consequences of either increased peroxides or a decline in the antioxidant defence.

Although increased generation of ROS before the onset of HBO-induced convulsions has been demonstrated in conscious rats, their production in association with oxygen toxicity has not been demonstrated satisfactorily in human subjects. There are increased electron spin resonance signals from blood of persons exposed to HBO but these return to normal within 10 min of cessation of exposure to HBO.

Pathology of Oxygen Toxicity

The pathology of oxygen toxicity has been documented comprehensively in a classical work on this topic (Balentine 1982). The various manifestations of oxygen poisoning are summarized in Figure 6.2. It is well known that the development of pulmonary and CNS toxicity depends upon the partial pressure and the duration of exposure, as shown in Figure 6.3. Fortunately, the early effects of poisoning are completely reversible, but prolonged expo-

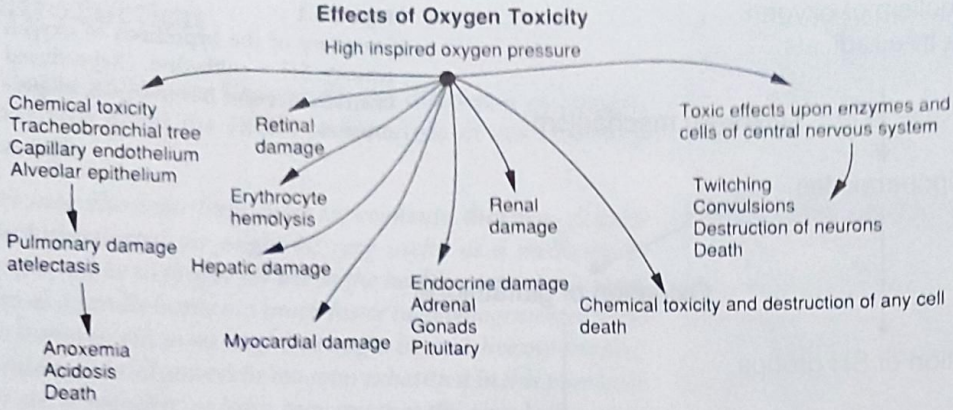

Figure 6.2
The effects of oxygen poisoning. (Reproduced from Clark 1974, by permission.)

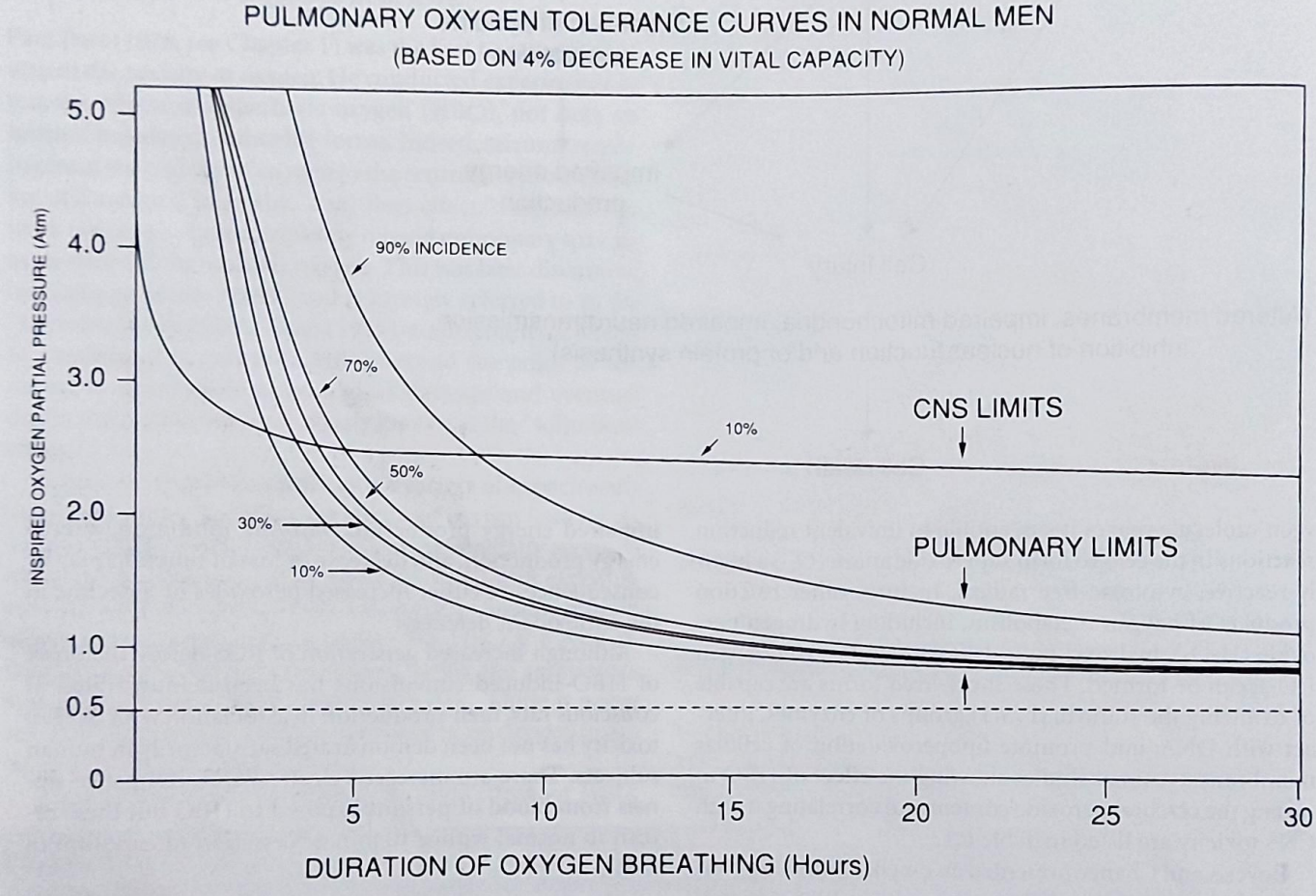

Figure 6.3
Individual variation in susceptibility to oxygen poisoning. Curves designated as pulmonary limits are inspired pO_2 exposure duration relationships for occurrence of one or more neurologic signs and symptoms listed in Table 6.5. (From Clark JM, Fischer AB: Oxygen toxicity and extension of tolerance in oxygen therapy. In Davis JC, Hunt TK (Eds.): Hyperbaric oxygen therapy, Bethesda, MD, Undersea and Hyperbaric Medical Society 1977. By permission.)

sure first lengthens the recovery period and then eventually produces irreversible changes. Many organs have been affected in experimental oxygen toxicity studies of long exposure to high pressures – a situation that is not seen in clinical practice.

High-pressure oxygen leads to increased pyruvate/lactate and pyruvate malate redox couples, as well as to a decrease in the incorporation of phospholipid long-chain fatty acid and pyruvate into the tissue lipid. During recovery from the effects of high-pressure oxygen these changes are reversed. These data indicate that oxygen poisoning of tissues is not the result of an inhibition of carbohydrate metabolism, but instead may result from the formation of toxic lipoperoxides.

The power expression for cumulative oxygen toxicity and the exponential recovery have been successfully applied to various features of oxygen toxicity at the Israel Naval Medical Institute in Israel (Arieli *et al* 2002). From the basic equation, the authors derived expressions for a protocol in which PO_2 changes with time. The parameters of the power equation were solved by using nonlinear regression for the reduction in vital capacity (DeltaVC) in humans:

$$\text{DeltaVC} = 0.0082 \times t_2\,(PO_2/101.3)(4.57)$$

where t is the time in hours and PO_2 is expressed in kPa.

The recovery of lung volume is:

$$\text{DeltaVC}(t) = \text{DeltaVC}(e) \times e(-(-0.42 + 0.00379\,PO_2)t)$$

where DeltaVC(t) is the value at time t of the recovery, DeltaVC(e) is the value at the end of the hyperoxic exposure, and PO_2 is the prerecovery oxygen pressure.

Data from different experiments on CNS oxygen toxicity in humans in the hyperbaric chamber were analyzed along with data from actual closed-circuit oxygen diving by using a maximum likelihood method. The parameters of the model were solved for the combined data, yielding the power equation for active diving:

$$K = t_2\,(PO_2/101.3)(6.8),$$

where t is in minutes.

It was suggested that the risk of CNS oxygen toxicity in diving can be derived from the calculated parameter of the normal distribution:

$$Z = [\ln(t) - 9.63 + 3.38 \times \ln(PO_2/101.3)]/2.02$$

The recovery time constant for CNS oxygen toxicity was calculated from the value obtained for the rat, taking into account the effect of body mass, and yielded the recovery equation:

$$K(t) = K(e) \times e(-0.079t)$$

where K(t) and K(e) are the values of K at time t of the recovery process and at the end of the hyperbaric oxygen exposure, respectively, and t is in minutes.

Pulmonary Oxygen Toxicity

This is usually a manifestation of prolonged exposure (more than 24 h) to normobaric 100% oxygen, as well as during exposure to HBO from 2 to 3 ATA O_2 in human and experimental animals. The pathology and pathophysiology of pulmonary oxygen toxicity are described in more detail elsewhere (Jain 1989b). The major mechanism by which HBO produces lung injury in rabbits is by stimulating thromboxane synthesis. Lung injury induced by free radicals has been demonstrated in an animal model of smoke inhalation, and the free radicals clear up after about an hour. Normobaric 100% oxygen given for one hour does not increase the level of free radicals in this model, but HBO at 2.5 ATA does so.

Acute changes in the lungs resulting from oxygen toxicity consist of alveolar and interstitial edema, alveolar hemorrhages, and proteinaceous exudates. This is followed by an inflammatory reaction. Further prolonged exposure to oxygen leads to a proliferative phase, which includes proliferation of type II epithelial cells and fibroblasts, followed by collagen deposits. Healing may occur after discontinuance of oxygen exposure, but areas of fibrosis and emphysema may remain. In patients with heart failure or in patients with reduced cardiac ejection fractions, HBO may contribute to pulmonary edema by increasing left ventricular afterload, increasing oxidative myocardial stress, decreasing left ventricular compliance by oxygen radical-mediated reduction in nitric oxide, increasing pulmonary capillary permeability, or by causing pulmonary oxygen toxicity (Weaver & Churchill 2001).

Repeated exposure to HBO at intervals insufficient to allow total recovery from pulmonary oxygen toxicity may lead to cumulative effects. The progression of toxicity can be monitored by serial pulmonary function studies. The concept of a "unit pulmonary toxic dose" (UPTD) has been developed (Bardin & Lambertsen 1970), and this allows comparison of the pulmonary effects of various treatment schedules of HBO (Table 6.2). The UPTD is designed to express any pulmonary toxic dose in terms of an equivalent exposure to oxygen at 1 ATA. It is only an arbitrary measure and does not allow for the recovery between HBO exposures. For example, 10 HBO treatments at 2.4 ATA for 90 min each would give the patient a UPTD of more than 200 and would indicate significant pulmonary toxicity with a 20% reduction in vital capacity. In practice, however, no clinical evidence of pulmonary toxicity is seen with this schedule. There is no significant impairment of pulmonary diffusing capacity in divers who have been intermittently exposed to HBO at 4 ATA for years.

Prolonged exposure to elevated oxygen levels is a frequent and important clinical problem. Superoxide dismutase (SOD) and catalase, the major intracellular antioxidant enzymes, cooperate in the detoxification of free oxygen radicals produced during normal aerobic respiration. Therapeutic approaches designed to deliver SOD or catalase to these intracellular sites would be useful in mitigating the pulmonary oxygen toxicity. A number of approaches to deliver these enzymes have not been successful. Adenovirus-mediated transfer to lungs of both catalase and SOD cDNA has been shown to protect against pulmonary oxygen toxicity. Distal airway epithelial cells, including type II alveolar and nonciliated bronchiolar epithelial cells, are important targets for oxygen radicals under the hyperoxic condition. The accessibility of these distal airway epithelial cells to *in vivo* gene transfer through the tracheal route of administration, suggests the

Table 6.2
Cumulative Pulmonary Oxygen Toxicity Indices for Commonly Used Oxygen Therapy Tables (Bardin & Lambertsen 1970)

Therapy table	UPTD[a]
• Chronic osteomyelitis/radionecrosis	
120 min oxygen at 33 fsw	300
90 min oxygen at 45 fsw	270
• Anaerobic infection	401
45 min oxygen/15 min air/45 min oxygen at 60 fsw	
45 min oxygen at 60–0 fsw with 8 min at 20 fsw and 27 min at 10 fsw	
• CO intoxication	445
45 min oxygen at 60 fsw	
30 min oxygen at 60–30 fsw	
15 min air/60 min oxygen at 30 fsw	
30 min oxygen at 30–0 fsw	
• USN 6	645
• USN 6 extended	
20 min oxygen/5 min air at 60 fsw	718
15 min air/60 min oxygen at 30 fsw	787
20 min oxygen/5 min air at 60 fsw and 15 min air/60 min oxygen at 30 fsw	860
• USN 6A	690
• USN 6A extended	
20 min oxygen/5 min air at 60 fsw	763
15 min air/60 min oxygen at 60 fsw	833
20 min oxygen/5 min air at 60 fsw and 15 min air/60 min oxygen at 30 fsw	906
• IFEM 7A (air and oxygen)	1813
• IFEM 7A alternating 50/50 Nitrox with air 30 min on/30 min off from 100–70 fsw	2061

[a] UPTD value indicates duration (min) of oxygen breathing at 1.0 ATA that would cause equivalent degree of pulmonary intoxication (measured as decrease in vital capacity)

potential for *in vivo* transfer of MnSOD and extracellular SOD genes as a future approach in the prevention of pulmonary oxygen toxicity (Tsan 2001).

Oxygen-Induced Retinopathy

Retrolental fibroplasia is considered to be an oxygen-induced obliteration of the immature retinal vessels when 100% oxygen is given to premature infants. A recent study showed that oxygen therapy for more than 3 days, in infants delivered following 32–36 weeks of gestation, was not associated with an increased risk of retinopathy of prematurity (Gleissner *et al* 2003). HBO (2.8 ATA, 80% oxygen) given to premature rats does not result in retinopathy, whereas control animals given normobaric 80% oxygen developed retinopathy. This topic is discussed further in Chapter 32.

Factors that Enhance Oxygen Toxicity

Various factors which enhance oxygen toxicity are listed in Table 6.3. Combining HBO with the substances listed, together with morbid conditions such as fever, should definitely be avoided.

Mild hyperthermia (38.5 °C) has been used therapeutically for a number of conditions. An increase of temperature increases oxygen uptake by body tissues. Hyperthermia may thus be expected to enhance oxygen toxicity. Transient biochemical side effects of mild hypothermia such as hyperammonemia can be inhibited by HBO, but this combination should be used cautiously to avoid oxygen toxicity.

It is generally believed that high humidity enhances oxygen toxicity as manifested by lung damage and convulsions. This has been experimentally verified in rodents exposed to HBO (515 to 585 kPa) under conditions of low humidity as well as 60% relative humidity.

Physical exercise definitely lowers the threshold for CNS oxygen toxicity in the rat over the entire range of pressures from 2 to 6 ATA. This observation should be kept in mind in planning physical exercise in hyperbaric environments (see Chapter 4). Various enzymes inhibited by hyperoxia are shown in Table 6.4. This may explain how hyperoxia leads to oxygen toxity.

Glutathione reductase is an integral component of the antioxidant defence mechanism. Inhibition of brain glutathione reductase by carmustine lowers the threshold for seizures in rats exposed to HBO.

Table 6.3
Enhancers of Oxygen Toxicity

- Gases
  - Carbon dioxide
  - Nitrous oxide
- Hormones
  - Insulin
  - Thyroid hormones
  - Adrenocortical hormones
- Neurotransmitters
  - Epinephrine and norepinephrine
- Drugs and chemicals
  - Acetazolamide
  - Dextroamphetamine
  - NH_4Cl
  - Paraquat
  - Aspirin
  - Disulfiram
  - Guanethidine
- Trace metals
  - Iron
  - Copper
- Morbid conditions
  - Fever
  - Vitamin E deficiency convulsions
  - Congenital spherocytosis
- Physiological states of increased metabolism
  - Physical exercise
  - Hyperthermia
  - Diving

Table 6.4
Enzymes Inhibited by Hyperoxia at 1–5 ATA

1. Embden-Meyerhof pathway
   - Phosphoglucokinase
   - Phosphoglucomutase
   - Glyceraldehyde-phosphate-dehydrogenase*
2. Conversion of pyruvate to acetyl-CoA
   - Pyruvate oxidase
3. Tricarboxylic acid cycle
   - Succinate dehydrogenase*
   - α-ketoglutarate dehydrogenase*
   - Malate dehydrogenase*
4. Electron transport
   - Succinate dehydrogenase*
   - Malate dehydrogenase*
   - Glyceraldehyde-phosphate dehydrogenase*
   - DPNH dehydrogenase*
   - Lactate dehydrogenase*
   - Xanthine oxidase
   - D-Amino acid oxidase
5. Neurotransmitter synthetic enzymes
   - Glutamic acid decarboxylase
   - Choline acetylase
   - Dopa decarboxylase
   - 5-HTP decarboxylase
   - Phenylalanine hydroxylase
   - Tyrosine hydroxylase
6. Proteolysis and hydralysis
   - Cathepsin
   - Papain
   - Unspecified proteases and peptidases
   - Unspecified in autolysis
   - Arginase
   - Urease
   - Ribonuclease
7. Membrane transport
   - NA^+, K^+-$ATPase^+$
8. Molecular oxygen reduction pathway
   - Catalase
9. Others
   - Acetate kinase
   - Cerebrosedase
   - Choline oxidase
   - Fatty acid dehydrogenase
   - Formic acid dehydrogenase
   - Glutamic dehydrogenase
   - Glutamic synthetase
   - Glyoxylase
   - Hydrogenase
   - Isocitrate lyase
   - Malate syntase
   - Myo kinase (adenylate kinase)
   - Phosphate transacetylase
   - Transaminase
   - Zymohexase (aldolase)

*Asterisks indicate enzymes containing essential sulfhydryl (SH) groups, emphasized as being inactivated by oxidation of these groups.

Central Nervous System Oxygen Toxicity

Effect on Cerebral Metabolism

Disturbances of cerebral metabolism resulting from hyperoxia have been described in Chapter 2. HBO at 2 ATA has been shown to stimulate rCMRGl slightly, but does not result in any toxic manifestations. Oxidative metabolism of the brain is usually not affected by pressures up to 6 ATA. In the primary rat cortical culture, HBO exposure to 6 ATA for 30, 60, and 90 min increased the lactate dehydrogenase (LDH) activity in the culture medium in a time-dependent manner (Huang *et al* 2000). Accordingly, the cell survival was decreased after HBO exposure. Pretreatment with the NMDA antagonist MK-801 protected the cells against the HBO-induced damage. The protective effect was also noted in the cells pretreated with L-N(G)-nitro-arginine methyl ester, an NO synthase inhibitor. These results suggest that activation of NMDA receptors and production of NO play a role in the neurotoxicity produced by HBO exposure.

There is no evidence that seizures are related to oxidative metabolic changes. However, increase of glucose utilization precede the onset of electrophysiological manifestations of CNS oxygen toxicity). Increased nitric oxide (NO) production during prolonged HBO exposure is responsible for escape from hyperoxic vasoconstriction in cerebral blood arterioles. The finding suggests that NO overproduction initiates CNS oxygen toxicity by increasing rCBF, which allows excessive oxygen to be delivered to the brain (Demchenko *et al* 2001). The hypothetical pathophysiologic pathways leading to acute and chronic CNS oxygen toxicity are illustrated in Figure 6.4.

Effect on Neurotransmitters

Neurotransmitters have been shown to be downregulated under hyperbaric hyperoxia (Courtiere *et al* 1991). With the recognition of nitric oxide (NO) as a neurotransmitter, its relationship to hyperia has been studied. Experimental studies of Zhang *et al* (1993) showed that rats can be protected against oxygen toxicity by a combination of a monoamine oxidase inhibitor and a nitric oxide (NO) synthase inhibitor. Their data showed that protection against oxygen toxicity by these agents is not related to the preservation of the GABA pool. They found that oxygen-dependent noradrenaline metabolism and NO synthesis appear to be inactive during oxygen neurotoxicity. Oury *et al* (1992) consider NO to be an important mediator in oxygen neurotoxicity and suggest that extracellular superoxide dismutase increases oxygen neurotoxicity by inactivation of NO.

Exposures to HBO at 2 and 2.8 ATA stimulated neuronal NO synthase (nNOS) and significantly increased steady-state

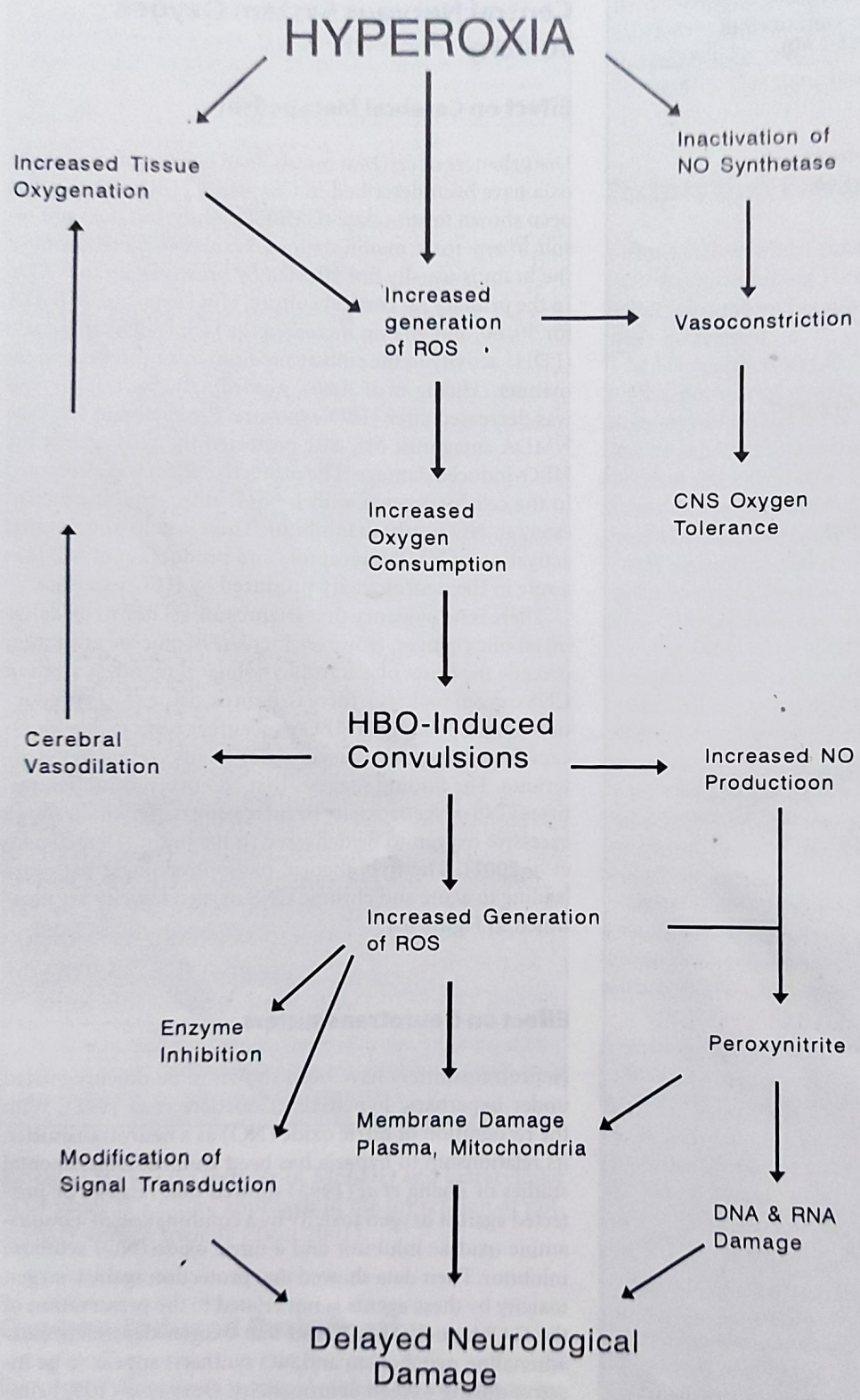

Figure 6.4
Basic mechanisms of CNS oxygen toxicity. ROS = reactive oxygen species, NO = nitric oxide (by D. Torbati, PhD).

(Thom *et al* 2003). At both pressures, elevations in NO concentration were inhibited by the nNOS inhibitor 7-nitroindazole and the calcium channel blocker nimodipine. Infusion of superoxide dismutase inhibited NO elevation at 2.8, but not 2 ATA HBO. Hyperoxia increased the concentration of NO associated with hemoglobin. These findings highlight the complexity of oxidative stress responses and may help explain some of the dose responses associated with therapeutic applications of hyperbaric oxygen.

Ammonia and Amino Acids

Single seizures induced in rats subjected to HBO at 6 ATA have been shown to be associated with accumulation of ammonia and alterations in amino acids in the brain, with the greatest changes taking place in the striatum (Mialon *et al* 1992). These changes were considered to be caused by an increase in oxidative deamination or possibly the result of glial failure to capture released amino acids. The subsequent imbalance between the excitatory and inhibitory mediators in the striatum was offered as an explanation of the recurrence of seizures in animals maintained on HBO.

Changes in the Electrical Activity of the Brain and Seizures

Conscious rats and rabbits exposed to HBO usually demonstrate an increased EEG slow wave activity which eventually develops into bursts of paroxysmal electrical discharges. These electrical events precede the onset of visible HBO-induced convulsions, and therefore were suggested as an early signs of CNS oxygen toxicity in experimental animals. *In vitro* studies with HBO also show changes in neuronal electrical activity, which may be associated with seizures.

The seizure associated with HBO usually occurs toward the end of the oxygen exposure while the patient is being decompressed. It is a violent motor discharge with a brief period of breathholding. In such cases, therefore, decompression should be temporarily halted until the seizure is over; otherwise there could be rupture of lung alveoli.

Oxygen-induced seizures are not a contraindication for further HBO therapy. Further HBO treatments may be carried out at lower pressures and shorter exposures. Anticonvulsant medications are usually not indicated, but may be used. In animal experiments Carbamazepine (Reshef *et al* 1991) and vigabatrin (Tzuk *et al* 1991) have been found to be effective in preventing HBO-induced convulsions. Acupuncture has been claimed to protect against oxygen-induced convulsions by increasing GABA in the brain levels (Wu *et al* 1992).

Epilepsy has been listed as a contraindication for using HBO therapy. This is based on the assumption that oxygen is liable to precipitate a seizure in an epileptic patient and such an event in a chamber might be detrimental to the patient. Seizures in epileptic patients are rare during HBO therapy where pressures less than 2 ATA are used. There is no published study that reexamines this issue. The question therefore still arises: is HBO really dangerous for an epileptic? If epilepsy is included in the contraindications for HBO, patients with head injuries and strokes who happen to have seizures would be deprived of the benefit of HBO therapy. The mechanism of epilepsy in such patients is different from that of an oxygen-induced convulsion. It has even been shown that EEG abnormalities in stroke patients improve with HBO treatment (Wassmann 1980). It is possible that HBO may abort a seizure from a focus with circulatory and metabolic disturbances by correcting these abnormalities. Seizures are extremely rare and no more than a chance occurrence during HBO sessions at pressures between 1.5 and 2 ATA even in patients with a history of epilepsy.

Neuropathology

In experimental studies, there is no damage to the CNS of rats exposed to HBO until the pressure exceeded 4 ATA. The brain damage is increased by CNS-depressant drugs, increase of pCO_2, acetazolamide, and NH_4Cl. Permanent spastic limb paralysis has been observed in rats (the John Bean effect) after repeated exposure to high oxygen pressures (over 5 ATA). There is selective necrosis of white matter both in the spinal cord and the brain, and this is considered to be the effect of hyperoxia. HBO-induced rat brain lesions, examined by electron microscopy, show two types of nerve cell alterations: (1) type A lesions characterized by pyknosis and hyperchromatosis of the nerve cells, vacuolization of the cytoplasm, and simultaneous swelling of the perineural glial processes; (2)type B lesions are characterized by lysis in the cytoplasm and karyorrhexis.

Manifestations of CNS Oxygen Toxicity

Signs and symptoms of CNS oxygen toxicity are listed in Table 6.5.

Clinical Monitoring for Oxygen Toxicity

The most important factor in early detection of oxygen toxicity is the observation of signs and symptoms. For monitoring pulmonary function, determination of vital capacity is the easiest and most reliable parameter, as it is reduced before any irreversible changes occur in the lungs. EEG

Table 6.5
Signs and Symptoms of CNS Toxicity

Facial pallor	Acoustic symptoms
Sweating	Music
Bradycardia	Bell ringing
Choking sensation	Knocking
Palpitations	Unpleasant olfactory sensations
Epigastric tensions	Unpleasant gustatory sensations
Sleepiness	Respiratory changes
Depression	Panting
Euphoria	Grunting
Apprehension	Hiccoughs
Changes of behavior	Inspiratory predominance
Fidgeting	Diaphragmatic spasms
Disinterest	Severe nausea
Clumsiness	Spasmodic vomiting
Visual symptoms	Vertigo
Loss of acuity	Fibrillation of lips
Dazzle	Lip twitching
Lateral movement	Twitching of cheek and nose
Decrease of intensity	Syncope
Constriction of visual field	Convulsions

tracings do not show any consistent alterations before the onset of seizures and are not a reliable method of early detection of oxygen toxicity.

Decrease in [9,10–^{3}H] oleic acid incorporation by human erythrocytes detected *in vitro* after HBO exposure *in vivo* may reflect an early event in the pathogenesis of oxygen-induced cellular injury and may be a useful monitoring procedure.

An increase in CBF velocity (BCFV) precedes onset of symptoms of oxygen toxicity during exposure to 280 kPa oxygen, which may be followed by seizure (Koch *et al* 2008). At rest a delay of approximately 20 min precedes the onset of CNS oxygen toxicity and seizure can be aborted with timely oxygen reduction.

Protection Against Oxygen Toxicity

Various agents and measures for prevention or treatment of oxygen toxicity are listed in Table 6.6; these are mostly experimental. The most promising agents are the antioxidants. The use of vitamin E (tocopherol) is based on the free-radical theory of oxygen toxicity. It has been used to protect premature infants (who lack vitamin E) against oxygen toxicity. Dietary supplementation with selenium and vitamin E, which increase the cerebral as well as extracerebral GSH content, does not protect rats against the effect of HBO by delaying the onset of first electrical discharge (Boadi *et al* 1991). However, such diets may still be advantageous in promoting recovery and reversal of toxic process, as occurs between consecutive HBO exposures or during intermittent oxygen exposure (Bleiberg & Kerem 1988).

Table 6.6
Factors Protecting Against Generalized Oxygen Toxicity

Antioxidants, free radical scavengers, and trace minerals
allopurinol
ascorbic acid
glycine
magnesium
selenium
superoxide dismutase, SOD
tyloxapol
vitamin E
Chemicals and enzymes modifying cerebral metabolism
arginine
coenzyme Q10 and carnitine
gamma-aminobutyric acid, GABA
glutathionehemocarnisine
interleukin-6
leukotriene B_4 antagonist SC-41930
paraglycine and succinic acid
sodium succinate and glutamate
Drugs
adrenergic-blocking and ganglion-blocking drugs
barbiturates
BCNU
chlorazepate
diazepam
ergot derivatives: lisuride and quinpirole
isonicotinic acid hydrazide
levodopa
lithium
milecide
MK-801 (a competitive NMDA receptor antagonist)
neuroleptics: chlorpromazine, thorazine
propranolol
Intermittent exposure to HBO
acclimatization to hypoxia
interposition of air-breathing periods
Endocrine factors
adrenalectomy
hypophysectomy
thyroidectomy
Gene therapy

Not all of the dietary free-radical scavengers are effective in counteracting oxygen toxicity. In animal experiments, no correlation was found between *in vitro* inhibition of lipid peroxidation and *in vivo* protection against oxygen toxicity.

Hypothermia has been considered to be a protector against oxygen toxicity, but HBO at 5 ATA induces hypothermia in mice, and this has little protective effect against convulsions.

Every clinician who treats patients should be aware of oxygen toxicity, although it is rare. At pressures of 1.5 ATA, even prolonged use in patients with cerebrovascular disease has not led to any reported case of oxygen toxicity. It should not be assumed that experimental observations regarding oxygen toxicity under hyperbaric conditions are applicable to normobaric conditions.

Whereas disulfiram protects against hyperbaric oxygen, it potentiates the toxicity of normobaric oxygen in rats. Ascorbic acid is also a free radical scavenger and protects against oxygen toxicity, but large doses of this vitamin may prove counterproductive in treating oxygen toxicity if the reducing enzymes are overloaded. An oxidized ascorbate might actually potentiate oxygen toxicity through lipoperoxide formation. Mg^{2+} has a double action against the undesirable effects of oxygen. It is a vasodilator and also a calcium blocker and protects against cellular injury. Magnesium sulfate suppresses the electroencephalographic manifestations of CNS oxygen toxicity and an anticonvulsant effect has been demonstrated in rats exposed to HBO at 6ATA. A prophylactic regimen of 10 mmol Mg^{2+} 3 h before a session of HBO and 400 mg of vitamin E daily, starting a couple of days before the HBO treatment, is useful in preventing oxygen toxicity, but no controlled study has been done to verify the efficacy of this regime.

The detoxifying function of cytochrome c to scavenge ROS in mitochondria has been confirmed experimentally (Min & Jian-xing 2007). A concept of mitochondrial radical metabolism is suggested based on the two electron-leak pathways mediated by cytochrome c that are metabolic routes of oxygen free radicals. The main portion of oxygen consumed in the electron transfer of respiratory chain is used in ATP synthesis, while a subordinate part of oxygen consumed by the leaked electrons contributes to ROS generation. The models of respiratory chain operating with two cytochrome c-mediated electron-leak pathways and a radical metabolism of mitochondria accompanied with energy metabolism are helpful in understanding the pathological problems caused by oxygen toxicity

Distal airway epithelial cells, including type II alveolar and nonciliated bronchiolar epithelial cells, are important targets for O_2 radicals under the hyperoxic condition. The accessibility of these distal airway epithelial cells to *in vivo* gene transfer through the tracheal route of administration, suggests the potential for *in vivo* transfer of MnSOD and extracellular SOD genes as a future approach in the prevention of pulmonary O_2 toxicity (Tsan 2001).

Extension of Oxygen Tolerance

Tolerance to oxygen primarily means tolerance to the toxic effects, because the physiological effects have no prolonged consequences. This subject has been discussed in detail by Lambertsen (1988). He considers a positive emphasis on extending oxygen tolerance as desirable, as opposed to a restrictive fear of oxygen poisoning. The following are compiled from his comments regarding extension of oxygen tolerance.

Tolerance Extension by Adaptation

At low levels of atmospheric hyperoxia, some forms of true protective adaptation appear to occur, such as that related to changing antioxidant defenses in some tissues. At higher oxygen pressures, some adaptation could conceivably occur in some cells of the intact human being with progressive and severe poisoning in other cells. At very high oxygen pressure, rapid onset of poisoning would make adaptation inadequate and too late.

Tolerance Extension by Drugs

A pharmacological approach, such as that of providing free radical scavengers, will attain broad usefulness only if the drug can attain the free permeability of the oxygen molecule. The drug should reach the right location at the right time, and remain effective there in the face of continuous hyperoxia, without itself inducing any toxic effects. There is no such ideal drug available at present.

Tolerance Extension by Interrupted Exposure to Oxygen

Interruption of exposure to HBO is known to extend the safe exposure time. In experimental animals, intermittent exposure to HBO postpones the gross symptoms of oxygen toxicity along with changes in enzymes, such as superoxide dismutase, in the lungs (Harabin *et al* 1990). Species differences were noted in this study; biochemical variables were more pronounced in guinea pigs than in rats.

There is no accepted procedure for quantifying the recovery during normoxia. A cumulative oxygen toxicity index – K, when K reaches a critical value (Kc) and the toxic effect is manifested, can be calculated using the following equation:

$$K = t_2e \times PO_2c$$

where t(e) is hyperoxic exposure time and PO_2 is oxygen pressure and c is a power parameter.

Recovery during normoxia (reducing K) is calculated by the following equation

$$K_2 = K_1 \times e[-rt(r)]$$

where t(r) is recovery time, r being the recovery time constant.

A combination of accumulation of oxygen toxicity and its recovery can be used to calculate central nervous system oxygen toxicity. Predicted latency to the appearance of the first electrical discharge in the electroencephalogram, which precedes clinical convulsions, was compared to mea-

sured latency for seven different exposures to HBO, followed by a period of normoxia and further HBO exposure (Arieli & Gutterman 1997). Recovery followed an exponential path, with r = 0.31 (SD 0.12) min (–1). Calculation of the recovery of the CNS oxygen toxicity agreed with the previously suggested exponential recovery of the hypoxic ventilatory response and was probably a general recovery process. The authors concluded that recovery can be applied to the design of various hyperoxic exposures.

Inclusion of air breaks in prolonged HBO treatment schedules is a recognized practice. The return to normobaric air between HBO sessions may lead to low pO_2 seizures, which are also described as a "switch off" phenomenon. However, much research still needs to be done to find the ideal schedules to extend oxygen tolerance.

Effect of HBO on the CNS of Newborn Mammals

Newborn mammals are extremely resistant to the CNS effects of HBO compared to adults. Indirect evidence indicates that HBO in newborn rats induces a persistent cerebral vasoconstriction concurrently with a severe and maintained reduction in ventilation. The outcome of these exposures may be as follows:

- Extension of tolerance to both CNS and pulmonary oxygen toxicity,
- Creation of a hypoxic-ischemic condition in vulnerable neuronal structures, and
- Impairment of circulatory and ventilatory responses to hypoxic stimuli on return to air breathing, with subsequent development of a hypoxic-ischemic condition.

These events may set the stage for development of delayed neurological disorders.

Conclusion and Directions for Future Research

The exact mechanism underlying oxygen toxicity to the CNS is not known, but the free radical theory appears to be the most likely explanation. The role of nitric oxide in the effect of HBO has also been established. Fortunately, CNS oxygen toxicity is rare because most HBO treatments are carried out at pressures below 2.5 ATA, and the duration of treatment does not exceed 90 min. Nevertheless, a physician treating patients with HBO must be aware of oxygen toxicity. There is no rational prevention or treatment, but free radical scavengers are used in practice to prevent the toxic effects of oxygen. Until a better understanding of the mechanism of oxygen toxicity and better methods of treatment are available, use of the free radical scavengers that are available appears to be a reasonable practice, particularly when these are relatively nontoxic. In situations where prolonged exposures to HBO are required, the benefits of treatment versus the risks of oxygen toxicity should be carefully weighed.

The chemiluminescence index, which is a measure of tissue lipid peroxidation indicates individual sensitivity of the body to HBO. Such a technique would enable the prediction of the effectiveness of HBO treatment as well as control its duration. Oxygen toxicity can also be exploited for therapeutic purposes. One example of this is the use of HBO as an antibiotic. Induced oxygen toxicity by HBO with protection of the patient by free radical scavengers should be investigated as an adjunctive treatment for AIDS, because the virus responsible for this condition has no protective mechanisms against free radicals. Since induction of antioxidative defence mechanisms has been determined after HBO exposure, a modified treatment regimen of HBO therapy may avoid genotoxic effects (Speit *et al* 2002).

The methods for estimating free radicals are still cumbersome and not in routine use. More practical methods should be developed as a guide to the safe limits of HBO therapy.

The molecular basis of oxygen toxicity should be sought at the cellular and organelle levels. Simultaneous monitoring of cerebral, electrical, circulatory, and energy-producing functions is a useful tool for determining the safety margins of HBO, as well as for tracing the primary mechanisms of oxygen toxicity in the CNS.

Mammalian cell lines have been shown to develop tolerance to oxygen by repetitive exposure to HBO at 6 to 10 ATA for periods up to 3 h. Repeated screening of various cell lines may lead to the discovery of oxygen-resistant cell types, which might provide an insight into the factors inherent in the development of oxygen tolerance.

The latest approach to counteract pulmonary oxygen toxicity is gene therapy by viral-mediated transfer SOD and catalase to the pulmonary epithelium. This appears to be the most promising method of delivery of these enzymes.