DEFINITION OF OXYGEN TOLERANCE IN MAN

In order to avoid the toxic effects of hyperoxia while fully exploiting each of its many potential applications, the rate of development of oxygen poisoning must be defined in man over a range of useful oxygen pressures. As indicated previously, the exposure durations at which a specific manifestation of oxygen poisoning occurs at different oxygen pressures can be described by a rectangular hyperbola (Fig. 6.6). This empirical observation was used in conjunction with a sensitive index of pulmonary oxygen poisoning to derive predictive curves which provided practical guidelines for many applications of hyperoxia (Clark & Lambertsen 1967, 1971a). Such predictive oxygen tolerance curves have been defined thus far only for the lung. The rationale and empirical basis for derivation of the existing pulmonary oxygen tolerance curves are summarized below. Areas are also indicated in which the ongoing analysis of new data (Lambertsen *et al.* 1987) is being used to improve the existing curves, as well as to derive similar oxygen tolerance curves for other organs and tissues.

Quantitative Indices of Pulmonary Oxygen Tolerance

The definition of oxygen tolerance in man requires the use of sensitive indices to monitor the onset and rate of progression of a toxic process that will ultimately be lethal. Several measures of pulmonary function were evaluated for this purpose in normal men who breathed O_2 at 2.0 ata (202 kPa) until they developed obvious subjective and objective manifestations of pulmonary oxygen poisoning (Clark & Lambertsen 1971b). The pulmonary function indices that were significantly altered at a completely reversible degree of intoxication included vital capacity, inspiratory capacity, expiratory reserve volume, inspiratory flow rate, carbon monoxide diffusing capacity and lung compliance.

A decrease in vital capacity proved to be the best available index for monitoring rate of pulmonary intoxication in groups of men. During oxygen breathing at 2.0 ata (202 kPa), it was reduced significantly at a time when symptoms were barely perceptible and it continued to fall throughout the exposure in association with increasing severity of symptoms (Clark & Lambertsen 1971b). It could be measured quickly and reproducibly in trained subjects. Furthermore, the fact that vital capacity had been measured in men exposed to hyperoxia by many different investigators (Table 6.3) provide data relevant to pulmonary oxygen tolerance over a wide range of oxygen pressures. None of the other measures of lung function that were altered in early pulmonary oxygen poisoning fulfilled all of the above criteria as well as decrease in vital capacity.

New information (Clark *et al.* 1987; Clark 1988a) obtained since the original derivation of pulmonary oxygen tolerance curves (Clark & Lambertsen 1967, 1970) has shown that no single measure of pulmonary function is uniquely satisfactory for monitoring either the rate of development of pulmonary oxygen poisoning or the post-exposure rate of recovery. For example, pulmonary mechanical function is impaired earlier and more severely than gas exchange function during continuous oxygen exposures over a range of useful pressures (Table 6.4), but pulmonary diffusing capacity for carbon monoxide appears thus far to be the most sensitive index of recovery from pulmonary oxygen poisoning (Fig. 6.19). Analysis and integration of this new information is in progress.

The Unit Pulmonary Toxic Dose Concept

Many practical applications of hyperoxia involve consecutive exposures to different oxygen pressures. Since oxygen poisoning occurs more rapidly at higher pressures, the same exposure duration does not produce equivalent degrees of intoxication at different levels of hyperoxia. The total dose of oxygen must therefore be described with respect to both the inspired Po_2 and the duration of exposure. This description can be facilitated by expressing exposures to different oxygen pressures in terms of an equivalent exposure to a standard reference level of hyperoxia. The 'unit pulmonary toxic dose' (UPTD) concept is designed to express any pulmonary toxic dose in terms of an equivalent exposure to O_2 at 1.0 ata (101 kPa; Bardin & Lambertsen 1970; Wright 1972).

UPTD calculations are based on vital capacity measurements that describe the rate of development of pulmonary intoxication at oxygen pressures above 0.5 ata (50 kPa). It is assumed that

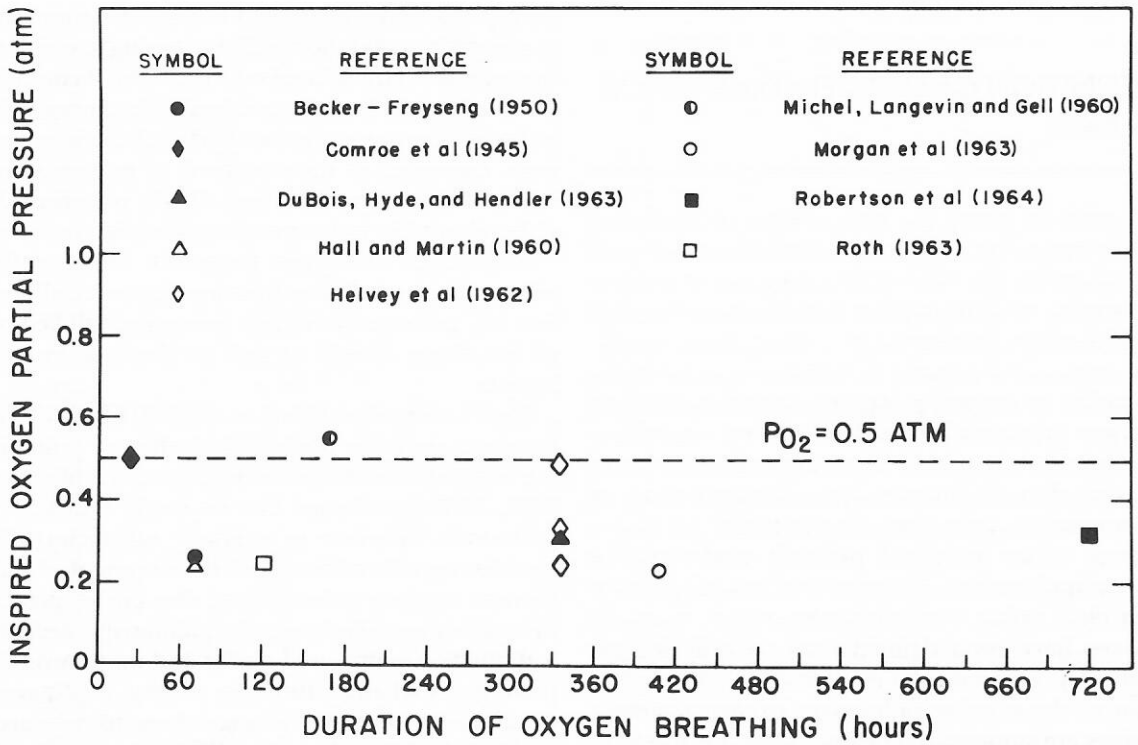

FIG. 6.21. Pulmonary oxygen tolerance studies in normal men which detected no objective evidence of pulmonary oxygen poisoning. Each symbol represents the average conditions of a separate study in man. The numbers of subjects in each study are listed in Table 6.3. (From Clark & Lambertsen 1970)

inspired P_{O_2}–exposure duration relationships for specific percentage decrements in vital capacity are rectangular hyperbolae, as found for other manifestations of oxygen poisoning (Fig. 6.6). It is further assumed that these hyperbolae describing pulmonary oxygen tolerance in man have vertical and horizontal asymptotes at zero time and 0.5 ata (50 kPa), respectively.

An asymptote at zero time implies that onset and progression of pulmonary intoxication are immediate at an infinitely high oxygen pressure. The horizontal asymptote at 0.5 ata (50 kPa) indicates that pulmonary function is not significantly impaired in men breathing oxygen at lower pressures. Its selection is based on the absence of detectable changes in vital capacity during exposures to the inspired P_{O_2}–duration conditions summarized in Fig. 6.21. Although the latter assumption cannot be made with certainty for indefinitely long exposures to low levels of hyperoxia, it is valid for at least 14 days at 0.49 ata (49 kPa; Helvey *et al.* 1962) and 30 days at 0.32 ata (32 kPa) of O_2 (Robertson *et al.* 1964).

A group of hyperbolic curves describing the time-course of pulmonary oxygen poisoning in man at pressures above 0.5 ata (50 kPa) is shown in Fig. 6.22. They are based on measurements of rate of decrease in vital capacity during oxygen breathing at 2.0 ata (202 kPa; Clark & Lambertsen 1971b), 1.0 ata (101 kPa; Caldwell *et al.* 1966) and 0.83 ata (83 kPa; Ohlsson 1947). Linear forms of the same curves on log–log co-ordinates are shown in Fig. 6.23. Data points representing the specified vital capacity changes in 50% of the exposed subjects at each of the three pressures are plotted in such a way that asymptotes will occur at zero time and 0.5 ata (50 kPa) inspired P_{O_2}. The oxygen tolerance curves are defined by drawing parallel lines through each set of three data points. Each line represents all of the inspired P_{O_2}–exposure duration combinations that produce the designated change in vital capacity or, stated in other terms, that represent an equivalent number of UPTD units. The reference standard for UPTD calculations is duration of oxygen breathing at 1.0 ata (101 kPa) expressed in minutes.

Each line in Fig. 6.23 can be described by the following general equation:

$$\log (P - 0.5\,\text{ata}) = m \log t + \log b$$

which is rewritten as

$$P - 0.5\,\text{ata} = bt^m$$

where P is inspired Po_2 (ata), t is exposure duration (min), b is the intercept constant on the pressure axis for $t = 1$, and m is the slope constant. The same equation may be used to convert any inspired Po_2–exposure duration combination (P_x, t_x) to an equivalent 1.0 ata exposure (P_1, t_1) as follows:

$$\frac{P_1 - 0.5\text{ ata}}{P_x - 0.5\text{ ata}} = \frac{bt_1{}^m}{bt_x{}^m}$$

Solving for t, gives:

$$t_1 = t_x^m \sqrt{\frac{P_1 - 0.5\,\text{ata}}{P_x - 0.5\,\text{ata}}}$$

When t is expressed in minutes and P_1 is given the value of 1.0 ata, t_1 becomes the number of UPTD units incurred by exposure (P_x, t_x). On the basis of available empirical data (Fig. 6.23), the slope constant is assigned a value of $m = -1.2$. Total UPTD units for consecutive exposures to more than one oxygen pressure are obtained by adding the units for each pressure.

Applications and Limitations of UPTD Predictions. The ability to predict the degree of pulmonary toxicity associated with a planned hyperoxic exposure facilitates the safe and effective use of oxygen in diving, decompression and therapy. For example, a diver should not be permitted to accumulate a large UPTD during a routine decompression, because repeated exposures to significant degrees of pulmonary intoxication will ultimately cause residual impairment of lung function. Furthermore, allowance should be made for additional hyperoxic exposure in the event that hyperbaric oxygen therapy is required for decompression illness near the end of the decompression period. A UPTD of 615 would be suitable for such an application. This is equivalent to a 2% decrement in vital capacity (Table 6.6), would probably be associated with only mild symptoms and

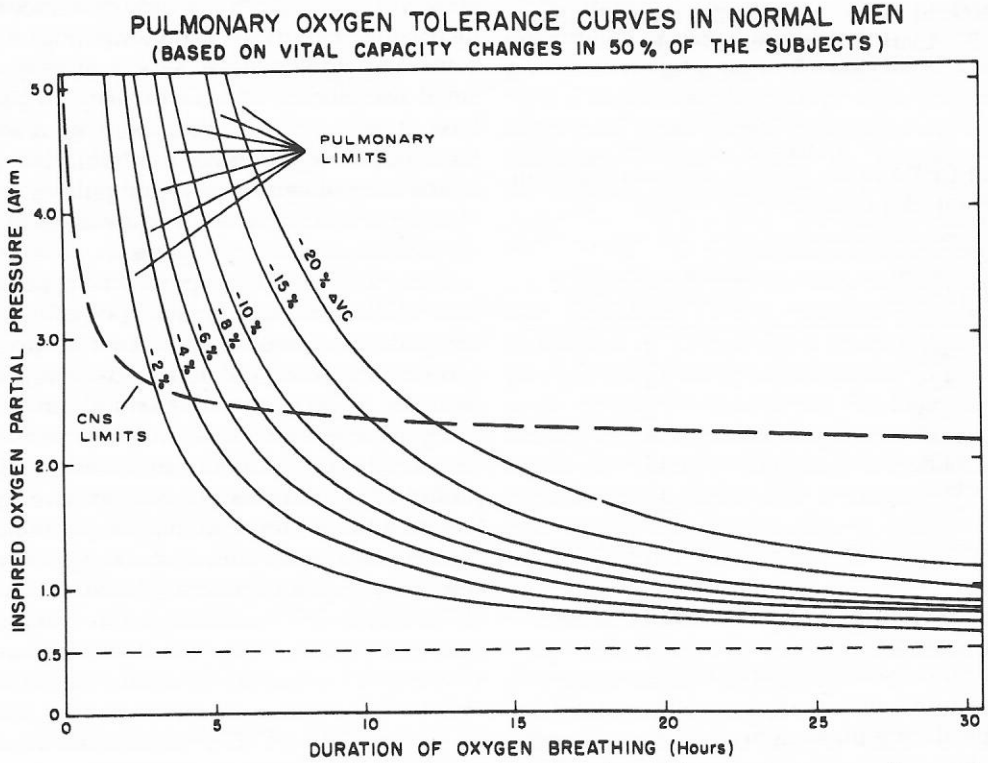

FIG. 6.22. Pulmonary and neurological oxygen tolerance curves for continuous exposures of normal men. The pulmonary limits represent vital capacity changes in 50% of the exposed subjects. The curve defining CNS limits represents a 10% incidence of neurological symptoms (Table 6.1). (Adapted from Lambertsen 1978)

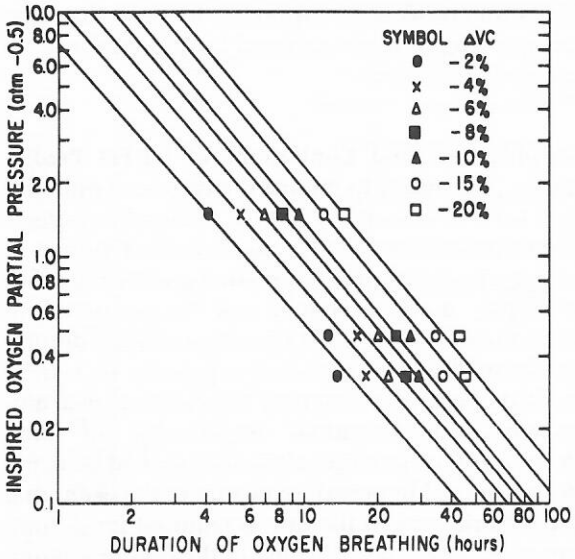

FIG. 6.23. Pulmonary oxygen tolerance curves on log–log co-ordinates. The hyperbolic curves shown in Fig. 6.22 are linear on logarithmic co-ordinates. Symbols represent the designated vital capacity decrements in 50% of the subjects studied by Clark and Lambertsen (1971b) at 2.0 ata (202 kPa), Caldwell *et al.* (1966) at 1.0 ata (101 kPa) and Ohlsson (1947) at 0.83 ata (83 kPa). See text for additional details. (From Clark & Lambertsen 1970)

TABLE 6.6
Equivalent UPTD values and average decrements in vital capacity (adapted from Wright 1972)

Equivalent UPTD units	*Average decrement in vital capacity (%)*
615	2
825	4
1035	6
1230	8
1425	10
1815	15
2190	20

would be completely reversible after cessation of hyperoxic exposure.

On the other hand, a UPTD of 1425, equivalent to a 10% decrement in vital capacity, would be permissible during the treatment of severe decompression illness, gas embolism or any other serious condition. Although this effect would also be expected to reverse completely, a longer recovery period would be required. Even larger UPTD levels which may be associated with residual impairment of pulmonary function are justifiable in the therapy of truly life-threatening conditions such as gas gangrene. Complete reversal of vital capacity decrements as great as 40–45% of the control volume have been observed after prolonged oxygen breathing at 2.0 and 2.5 ata (202 and 252 kPa; Clark & Lambertsen 1971b; Clark 1988a). However, it would be unwise to assume that all individuals will recover fully from comparable degrees of toxic effect, especially when such effects are produced by prolonged oxygen exposures at 2.0 ata (202 kPa) or lower.

Although the UPTD system has been used widely to provide guidelines for safe hyperoxic exposure in commercial and military diving operations (Flynn *et al.* 1981; Lemaire 1981; Edmonds *et al.* 1984), it still has the limitations that were recognized by its originators (Bardin & Lambertsen 1970; Wright 1972). Vital capacity decrements in any individual (Fig. 6.17) may be smaller or larger than the changes in 50% of the subjects on which UPTD predictions are based. A progressive decrease in vital capacity is usually associated with increasing severity of symptoms (Fig. 6.16), but some individuals have severe symptoms with small decrements in vital capacity, while others have prominent reductions with minimal symptoms (Clark & Lambertsen 1971b). The possible interactions of neurological and pulmonary effects of oxygen toxicity in some individuals (Fig. 6.20) also deviate from average data.

Even more critical in operational applications of the UPTD concept is the persisting lack of adequate data describing rate of recovery from various degrees of pulmonary oxygen poisoning. An early awareness of this critical limitation and recognition of individual variability in the rate of recovery from pulmonary intoxication (Fig. 6.17) prompted a purposefully conservative approach based on the assumption that the pulmonary toxic dose is cumulative, with no recovery between successive hyperoxic exposures (Bardin & Lambertsen 1970; Wright 1972). Although this certainly leads to over-estimation of toxic dose (Lemaire 1975; Gardette & Lemaire 1977), such an error is preferable to dangerous over-exposure of an individual on the basis of a UPTD prediction that assumes an unrealistically rapid recovery rate.

Recovery rates for several indices of pulmonary function were recently measured after early, rever-

sible degrees of pulmonary oxygen poisoning were produced by continuous oxygen exposures at 1.5, 2.0 and 2.5 ata (151, 202 and 252 kPa; Clark *et al.* 1987; Clark 1988a). The results show that selected indices of pulmonary mechanical function returned to pre-exposure levels within 15–30 h (Fig. 6.18), while an index of gas exchange function required more than 1 week for complete reversal of clinically benign but statistically significant changes (Fig. 6.19). In addition to the need for more information about rates of recovery from acutely evident, reversible degrees of pulmonary oxygen poisoning, an equally important information gap is that concerning the chronic, long-term effects of repeated exposures to subclinical or mild degrees of pulmonary intoxication.

Using an expanded data set which included vital capacity measurements (Eckenhoff *et al.* 1987) that were not available when the UPTD concept was originally developed (Bardin & Lambertsen 1970), Harabin *et al.* (1987) performed non-linear least-squares error analysis to assess statistically the variability of the available data and to calculate new constants for the predictive equations. Individual vital capacity data were fitted to the general hyperbolic equation:

$$\%\Delta VC = B_s(Po_2 - B_1)\,(t - B_2)^B_3$$

where Po_2 is inspired oxygen pressure in ata, t is exposure time in min, B_1 is the Po_2 asymptote, B_2 is the time asymptote, B_3 is an exponent that was empirically set to be -1.2 by Bardin and Lambertsen (1970; with rearrangement the sign of B_3 is positive) and B_s is an individual slope parameter. The overall statistical best fit of all individual data was obtained when the following conditions were met: (1) an individual slope parameter B_s was estimated for each subject rather than an average slope; (2) the Po_2 asymptote $B_1 = 0.38$ rather than 0.5 ata; (3) the time asymptote B_2 was essentially zero as before; and (4) exponent $B_3 = 1.0$ rather than 1.2. The slope parameter exerted the largest influence on the model, with the exponent and Po_2 asymptote exerting statistically significant but much smaller influences. For an individual of median susceptibility, the best fit of all data was obtained with the following equation:

$$\%\Delta VC = -0.009(Po_2 - 0.38)t$$

Recognizing that the Po_2 asymptote could not be estimated precisely even with the availability of new data, Harabin *et al.* provided the following alternative equation which incorporated the original Po_2 asymptote of 0.5 ata with essentially no loss in predictive capabilities:

$$\%\Delta VC = -0.011(Po_2 - 0.5)t$$

where Po_2 is given in ata and time in min. The methods used by Harabin *et al.* are essentially statistical tools for testing the overall consistency of available data. To the extent that limitations of the original UPTD concept are imposed by the individual variability and lack of total consistency of available data, non-linear least-squares analysis provides an objective, quantitative means for describing data interrelationships and assessing individual variability. However, no original data are provided. Limitations of the UPTD concept that arise from the lack of sufficient information can be ameliorated only by the appropriate design and performance of new experiments.

Need for an Objective, Pre-convulsive Index of CNS Oxygen Tolerance

The onset times for the symptoms and signs of CNS oxygen poisoning (Table 6.1) have been determined in large numbers of men at oxygen pressures ranging up to 7.0 ata (707 kPa; Haldane 1941; Donald 1947; Yarbrough *et al.* 1947; Butler & Thalmann 1984, 1986). However, many of the observed symptoms such as apprehension and nausea had no relationship to incipient convulsions, and signs such as muscle twitching, which did indicate that convulsions were imminent, did not always occur prior to the actual seizure. Butler and Thalmann (1986) classified the signs and symptoms of CNS oxygen toxicity that were experienced by their divers as 'probable' or 'definite' in an attempt to compensate for their varying reliability as harbingers of incipient convulsions. The actual occurrence of convulsions was placed in a third category. Butler and Thalmann (1984, 1986) also found that some divers appeared to be unusually susceptible to oxygen convulsions, and attempted to take this into account in their recommended limits for closed circuit oxygen diving (Table 6.2). Although convulsions are considered to be an undesirable index of CNS oxygen poisoning, it is not always possible to avoid them even under controlled laboratory conditions, and extensive investigation has revealed no evidence of residual neurological impairment (Lambertsen 1978).

Electroencephalography has been studied as an objective index of CNS oxygen poisoning (Gibbs *et al.* 1935; Cohn and Gersh 1945), but EEG alterations prior to the onset of convulsions could not be demonstrated. This early observation was recently confirmed by failure to detect any preconvulsive changes in brain cortical electrical activity, as measured with 12 scalp electrodes using the International 10–20 System, in one subject who convulsed after breathing O_2 at 3.0 ata (303 kPa) for 3 h (Lambertsen *et al.* 1987). The same subject had normal hearing thresholds and no detectable impairment of cognitive and psychomotor performance at pre-convulsive intervals of 4 and 30 min, respectively.

In lieu of a better toxicity index, the occurrence of a 10% incidence of neurological symptoms during exposure to oxygen pressures of 2.8–4.0 ata (282–404 kPa; Donald 1947; Yarbrough *et al.* 1947) was used to describe CNS oxygen tolerance in man (Fig. 6.22). Asymptotes for this curve were considered to be zero time and an inspired oxygen pressure of 2.0 ata (202 kPa). The latter asymptote was selected because no prominent neurological effects were observed in normal men breathing O_2 at 2.0 ata (202 kPa) for up to 12 h (Clark & Lambertsen 1971b). Although the absence of convulsions during similar oxygen exposures at 2.0 ata (202 kPa) was recently confirmed (Lambertsen *et al.* 1987), reversible decrements in the retinal electrical activity in response to a light flash (ERG b-wave amplitude) have been observed consistently (Clark *et al.* 1988, 1991a). At the present time, it appears that loss of peripheral vision (Fig. 6.13) and decrease in ERG b-wave amplitude are the best available quantitative indices of CNS oxygen toxicity for use in the development of improved CNS oxygen tolerance curves.

EXTENSION OF OXYGEN TOLERANCE

The onset and rate of progression of oxygen poisoning *in vivo* can be influenced by a variety of conditions, procedures and drugs (Clark & Lambertsen 1971a). Two major purposes for which these influences have been studied are the evaluation of their possible involvement in potential mechanisms of oxygen toxicity and the search for effective means of delaying the onset and decreasing the severity of intoxication in practical applications of hyperoxia. Limitations of space do not allow a discussion of the numerous factors that are known modifiers of the rate of development of oxygen poisoning. The effects of a large number of specific influences have been described in previous reviews (Haugaard 1968; Clark & Lambertsen 1971a; Deneke & Fanburg 1980; Frank & Massaro 1980; Clark 1982). Several potential means for the extension of oxygen tolerance were discussed in a recent symposium (Clark 1988b).

Any chemical agent that effectively delays the onset and progression of oxygen poisoning would be extremely useful in therapeutic and operational diving applications of hyperoxia. For maximal effectiveness, however, such an agent would have to be distributed throughout all body tissues to counteract the multiple, diverse effects of oxygen toxicity (Fig. 6.1), while at the same time remaining free of significant side-effects (Lambertsen 1978, 1988). For all of these reasons, the protective agents cited in previous reviews (Haugaard 1968; Clark & Lambertsen 1971a; Deneke & Fanburg 1980; Frank & Massaro 1980; Clark 1982) probably have only limited potential for practical applications.

An example of a chemical agent that was found initially to delay some of the effects of oxygen toxicity, but later actually proved to enhance the progression of other effects, is provided by disulfiram, a drug used in alcohol aversion therapy. Early studies showed that disulfiram administration effectively delayed the onset of convulsions and lung damage in animals exposed to O_2 at 4.0 ata (404 kPa; Faiman *et al.* 1971, 1974). The drug appeared to be promising for use in man, because even large doses were nearly devoid of toxic effects (Ritchie 1975). However, continued investigations showed that survival time is significantly decreased in rats given disulfiram before exposure to O_2 at 1.0 ata (101 kPa; Deneke *et al.* 1979) or 2.0 ata (202 kPa; Forman *et al.* 1980). This detrimental action of disulfiram is apparently caused by its metabolism *in vivo* to diethyldithiocarbamate, an inhibitor of superoxide dismutase (Forman *et al.* 1980).

Oxygen Tolerance Extension by Alternating Hyperoxia and Normoxia

In contrast to the present lack of truly effective pharmacological measures for extension of oxygen

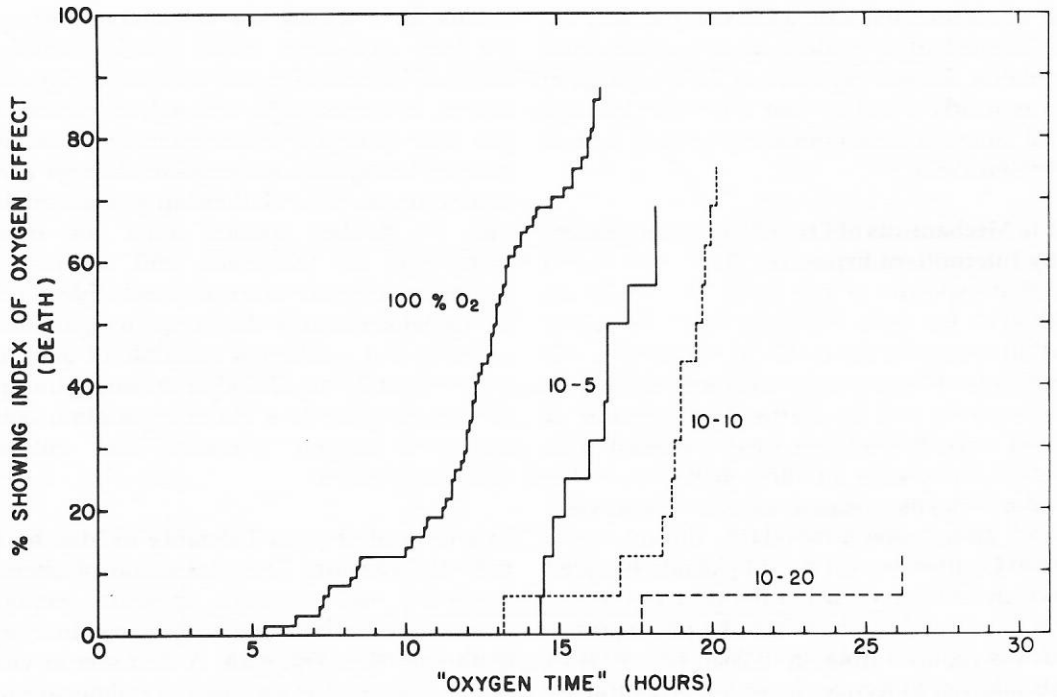

FIG. 6.24 Survival time in guinea-pigs during continuous and intermittent oxygen breathing at 3.0 ata (303 kPa). Oxygen time on the abscissa does not include intervals of normoxic exposure (7% O_2 in N_2 at 3.0 ata). (From Hall 1967)

tolerance, a currently useful procedure employs systematic alternation of hyperoxic exposure intervals with relatively brief normoxic intervals to increase markedly the total duration of tolerable exposure to a selected level of hyperoxia within a period of 24 h or longer (Lambertsen 1955, 1978, 1988; Hall 1967; Clark & Lambertsen 1971a; Clark 1974; Widell *et al.* 1974; Hendricks *et al.* 1977; Harabin *et al.* 1988). Since this procedure involves the periodic, sequential elevation and reduction of oxygen tension rather than passage of a chemical agent across cellular membrane barriers, it is effective in all organs and tissues affected by oxygen poisoning. Although the rates of reversal of the effects of oxygen toxicity (Fig. 6.1) are not known, the observation that oxygen tolerance can be extended significantly by alternating intervals of normoxia for 5 min with hyperoxia for 20 min (Hall 1967; Widell *et al.* 1974; Hendricks *et al.* 1977) indicates that substantial recovery must occur more rapidly than the corresponding rates of development.

Defining Optimal Principles of Oxygen Tolerance Extension by Intermittent Exposure. The quantitative gains in oxygen tolerance achieved by intermittent insertion of normoxic intervals ranging from one-half to double the length of the hyperoxic interval in guinea-pigs exposed to O_2 at 3.0 ata (303 kPa) are shown in Fig. 6.24. The oxygen time indicated on the abscissa for intermittent exposure represents the sum of all the oxygen breathing intervals. Survival time is increased progressively as the normoxic interval is lengthened while holding the oxygen period constant.

Subsequent experiments were designed to define optimal principles of oxygen tolerance extension in the rat by measuring survival time responses to systematically varied intermittent exposure patterns at oxygen pressures of 2.0 and 4.0 ata (202 and 404 kPa; Clark & Lambertsen 1982, 1989). In general, oxygen:normoxic exposure patterns with the same ratio, i.e. 20:20 and 60:60 min or 20:10 and 60:30 min, provided similar extensions of survival time at either 2.0 or 4.0 ata (202 or 404 kPa). This general rule did not apply when the oxygen period was so long that toxic effects were not readily reversible or when the normoxic interval was too short for adequate recovery from the preceding oxygen period. When a 60 min oxygen

period was alternated with a 180 min recovery interval, 20 rats had no evident adverse effects from a cumulative oxygen exposure at 2.0 ata (202 kPa) that was nearly equal to four times the average survival time for continuous exposure (Clark & Lambertsen 1982).

Possible Mechanisms of Oxygen Tolerance Extension by Intermittent Exposure. Frank *et al.* (1989) found that exposure of rats to O_2 at 0.95–1.0 ata (96–101 kPa) for 48 h, followed by a 24 h 'rest period' in air, made them able to tolerate 3–7 additional days of O_2 exposure with only slight pulmonary oedema and no deaths. The induction of increased oxygen tolerance was associated with significant increments in lung activities of the antioxidant enzymes, superoxide dismutase, catalase and glutathione peroxidase, during re-exposure to O_2 after the rest period. All rats survived re-exposure to O_2 even when the recovery period in air was reduced to 6 h. When the pre-exposure period was reduced from 48 to 36 h, only 83% of the rats allowed to recover in air for 24 h survived re-exposure for 3 days, and the survivors had macroscopic evidence of pulmonary damage. These results are relevant to possible mechanisms of oxygen tolerance extension by intermittent exposure, because they demonstrate that a sufficiently toxic oxygen exposure, followed by a suitable normoxic recovery period, induces the production of antioxidant enzymes upon subsequent exposure to hyperoxia.

Harabin *et al.* (1990) measured brain and lung antioxidant enzyme responses in guinea-pigs and rats that were exposed either continuously to O_2 at 2.8 ata (282 kPa) or intermittently on a schedule that alternated 10 min oxygen periods with 2.5 min periods of air breathing (0.56 ata O_2; 57 kPa). The convulsion and survival times were significantly longer during intermittent exposure than for continuous exposure in both species. The antioxidant enzyme activities in the brain and lung were compared at equivalent durations of continuous and intermittent oxygen exposure. Brain superoxide dismutase (SOD) activity was not significantly changed in either species. Catalase (CAT) activity was reduced in guinea-pigs during both continuous and intermittent exposures. Glutathione peroxidase (GSHPx) activity was reduced in both species for both types of exposure. Lung SOD activity was increased during intermittent exposure in guinea-pigs and during both exposures in rats. CAT activity was reduced in both species for both exposures, while GSHPx activity was reduced for both exposures in guinea-pigs, but not in rats. In guinea-pigs, antioxidant enzyme activities were generally either increased more or decreased less during intermittent than for continuous exposure. This relationship was less evident in rats. In neither species could the observed increments in convulsion and survival times during intermittent exposure be attributed primarily to changes in antioxidant enzyme activities. It is possible that a different schedule of intermittent exposure at 2.8 ata (282 kPa) or some other pressure would provide a closer association between increased oxygen tolerance and antioxidant enzyme activities.

Extension of Oxygen Tolerance in Man by Intermittent Exposure. The application of alternating hyperoxic and normoxic exposure periods to extension of pulmonary oxygen tolerance in man is illustrated in Fig. 6.25. A decrease in vital capacity was used as an index of pulmonary intoxication in men breathing O_2 at 2.0 ata (202 kPa; Hendricks *et al.* 1977). The results obtained for alteration of 20 min oxygen and 5 min normoxic periods are compared with similar measurements obtained during continuous exposure of a different group of subjects to O_2 at 2.0 ata (202 kPa; Clark & Lambertsen 1971b). The comparison indicates that duration of oxygen breathing associated with a 4% decrement in vital capacity is more than doubled by the use of intermittent exposure.

For the purpose of testing in man the principle that equivalent gains in oxygen tolerance are provided by intermittent exposure patterns that have the same oxygen:normoxic ratio, vital capacity was measured repeatedly in six subjects who were exposed to O_2 at 2.0 ata (202 kPa) on an intermittent exposure pattern that alternated 60 min oxygen periods with 15 min normoxic intervals (Clark *et al.* 1990). The degree of oxygen tolerance extension provided by the 60:15 intermittent exposure pattern was then compared with that found for the 20:5 pattern previously used by Hendricks *et al.* (1977). The rate of vital capacity reduction in four of the six subjects on the 60:15 pattern was nearly identical to the average rate of fall in five subjects on the 20:5 pattern, but vital capacity fell more rapidly in the remaining two subjects. These results are consistent with the interpretation that optimal use of intermittent ex-

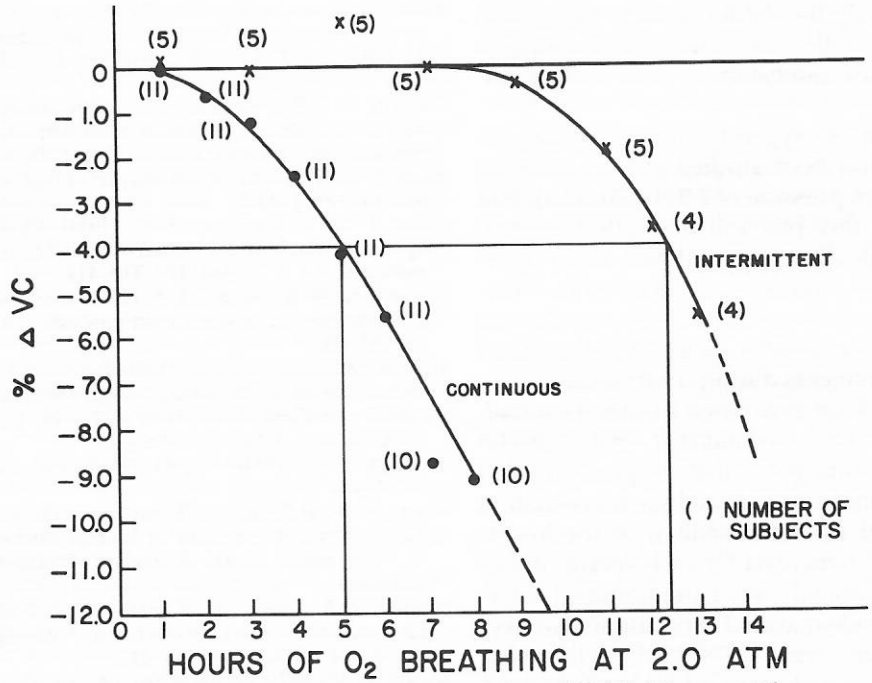

FIG. 6.25. Extension of pulmonary oxygen tolerance at 2.0 ata (202 kPa) in man. The curve showing rate of decrease in vital capacity during continuous oxygen breathing was obtained from Clark and Lambertsen (1971b). The curve for intermittent oxygen exposure was adapted from Hendricks *et al.* (1977), and the indicated duration of oxygen breathing represents a summation of all of the intermittent, 20 min oxygen periods

posure to extend pulmonary oxygen tolerance in man at 2.0 ata (202 kPa) will require the use of oxygen exposure periods that are less than 60 min in duration (Clark *et al.* 1990).

Prior to the recently completed exposures on a 60:15 intermittent pattern at 2.0 ata (202 kPa), extension of oxygen tolerance by intermittent exposure was confirmed only for the lung. Using progressive reduction in the ERG b-wave amplitude as an index of toxic effects on the visual system, nearly equivalent degrees of oxygen tolerance extension were found for both the eye and the lung in the same subjects (Clark *et al.* 1991a). The progressive decline in average b-wave amplitude preceded the average fall in vital capacity for both continuous and intermittent oxygen exposure at 2.0 ata (202 kPa).

An early concept of the basis for oxygen tolerance extension by intermittent exposure indicated that the cumulative oxygen exposure required to produce overt manifestations of oxygen poisoning can be lengthened by periodic reversal of the subclinical toxic effects that develop during each successive oxygen exposure period (Lambertsen 1955). Although this concept has not been refuted, a recent comparative evaluation of two different patterns of intermittent oxygen exposure at 2.0 ata (202 kPa) indicates that an additional pathway of oxygen tolerance extension must be involved (Clark *et al.*, 1992). Visual and pulmonary indices of oxygen poisoning were measured repeatedly in two groups of subjects who were exposed intermittently on either a 60:15 or a 30:30 pattern. The latter pattern was expected to provide greater extensions of oxygen tolerance, because it simultaneously halved the oxygen exposure period and doubled the normoxic recovery interval. The expected results were in fact observed at the end of about 14 oxygen exposure hours, but the toxic effects associated with the 30:30 pattern exceeded those for the 60:15 pattern at an earlier duration of exposure when expressed in terms of oxygen hours. This apparent early development and later reversal of overt toxic effects on the 30:30 pattern must reflect the existence of an additional, previously undetected pathway for oxygen tolerance extension by intermittent exposure. Although the nature of this additional pathway is not yet

known, it is likely that better understanding will provide opportunities for even greater gains in oxygen tolerance extension by intermittent exposure.

The extension of oxygen tolerance by intermittent exposure has been studied in man thus far only at an oxygen pressure of 2.0 ata (202 kPa). Full exploitation of this practical and effective procedure in therapeutic and operational applications of hyperoxia will require similar studies in a variety of organs and tissues (Table 6.5) over a range of useful oxygen pressures. Some of the required baseline measurements during continuous oxygen exposures have been performed (Lambertsen *et al.* 1987; Clark *et al.* 1987; Gelfand *et al.* 1987; Pisarello *et al.* 1987). It is anticipated that the greatest gains in oxygen tolerance and applied hyperoxygenation will be achieved by determination of the lowest effective level of hyperoxia for each specific application and by optimal use of programmed intermittency to provide maximal exposure to that oxygen pressure (Lambertsen 1978, 1988). In the event that effective, non-toxic antioxidant drugs become available for administration to man, it is likely that their greatest usefulness will be in conjunction with intermittent exposure rather than in lieu of it.

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