Chapter 8

Treatment and General Hyperbaric Limitations

The formulation of a decompression and the overall planning of a dive is not solely determined by the imminence of decompression sickness. There are factors which limit the rate of compression, the composition of the mixture breathed on the 'bottom' and then the use of agents such as oxygen for both prevention and treatment of bends. In addition, there are a number of hyperbaric phenomena which have been observed scientifically but are better discussed separately since it is not certain that they are responsible for the clinical effects or have any clinical manifestations at all. However, the most serious clinical consequences of diving, second only to neurologic and spinal decompression sickness, are those of dysbaric osteonecrosis ('bone rot'). Although it is not yet known how a dive can be modified to prevent it, or even whether it can be prevented at all, enough information is starting to accumulate to enable some prediction of its incidence to be made.

Dysbaric Osteonecrosis

There is now little doubt that aseptic necrosis of bone can be caused by exposure to compressed air, since the incidence is several orders of magnitude higher in caisson workers and divers than in the normal population. In this text the view has been taken that this insidious occupational hazard is better considered alone, since it is not certain that it is the result of inadequate decompression that many assume it to be; while certain pathological studies indicate that bends and bone necrosis may result from different disease processes (Rozsahegyi, 1956). Large epidemiological surveys have been completed and the clinical course of dysbaric osteonecrosis is now quite well documented along with some comprehensive studies of the general pathology. However, the basic mechanism remains unknown and hence the means of prevention. This fact is not aided by the general lack of fundamental knowledge of the physiology of bone—a most complex organ—which in the past has all too often been viewed as just the mineral 'coathanger' for the physiological system.

Symptomatology

Most of the standard clinical texts on dysbaric osteonecrosis immediately plunge the reader into the radiographic language of 'segmental and linear opacities', 'snow-caps', etc., needed to describe bone lesions. However, these are essentially irregularities from what is considered normal or non-pathological in an X-ray of that bone and require interpretation not only by qualified radiologists but by those radiologists familiar with the characteristics of long-bone surveys peculiar to divers and caisson workers. For the best descriptions of the early diagnosis of dysbaric osteonecrosis, the reader is therefore referred to the work of Golding *et al.* (1960), Davidson (1964), Harrison (1971, 1974), Fagan *et al.* (1974) and several reports published by the Decompression Panel of the Medical Research Council (MRC) in London (1966, 1971, 1974). For those seeking a more introductory text to the radiographic appear-

ance of bone lesions, the reader is referred to the superb atlas of high-quality X-rays and accompanying case histories produced by Griffiths at the MRC's Registry in Newcastle.

Lesions have been reported in the long bones of caisson workers almost from the time that X-ray machines were invented at the turn of the century. Essentially they are recognized as regions of abnormal opacity, those less dense than normal representing sequestration of mineral, while denser regions indicate mineral deposition—regrowth of new bone on to dead trebeculae which are the mineral 'skeletons' remaining after death of the cells. Hence radiographic evidence may be quite a late indication of the onset of osteonecrosis.

The disease follows no specific course and, when once initiated, may start or stop at any time related in no obvious way to any history of continuing exposure to compressed air. Lesions occur in both the shaft and the ends of the bones—particularly the long bones. Most remain asymptomatic but where they progress to any appreciable extent close beneath the articular surface of a joint (a juxta-articular lesion), the disease may cause the weight-bearing surface to collapse. This may occur slowly, when it is often incorrectly diagnosed as arthritis, or suddenly as in the case of the tunnel worker who has just started to lift a heavy beam or bag of tools as his job demands. Although some surgeons may go to enormous lengths to repair such damage (Jones, 1974) the majority of these manual workers remain disabled, while prostheses have a limited life—a major problem in a young tunnel worker or diver in which these are feasible. Detailed descriptions of the management of these cases include those of Walder (1974) and Barnes (1967).

Incidence

Massive epidemiological surveys of British caisson workers of which there are now some 1,500–2,000 registered with the MRC Registry, some followed for as long as 12 years, have indicated an overall incidence of radiographically identifiable lesions as about 20% (MRC, 1975). However, such lesions may be found in at least 50% of those men who have worked regularly in compressed air over a number of years. Of the total showing some form of aseptic osteonecrosis, this occurs in disabling juxta-articular sites in about 17% but sometimes up to 49% (Davidson and Griffiths, 1970) or even 71% (Nellen and Kindwall, 1972).

In divers, the overall incidence of radiographically identifiable bone lesions tends to vary more widely, ranging from 2% in the U.S. Navy (Peck, 1974) and 6% in the Royal Navy (Elliott and Harrison, 1970) up to 27% for commercial diving in the Gulf of Mexico (Fagan *et al.*, 1974). This probably reflects the amount of actual diving performed by these men since, for professionals with at least ten years in the industry, there are reports of incidences as high as 50% in Japan (Ohta and Shigeto, 1969) and 55% in Germany (Alnor, 1963). However, these figures should only be taken as a rough guide, since different diagnostic criteria could have been used by the radiologists employed in each survey.

Features

The major problem in elucidating the mechanism of dysbaric osteonecrosis is the delay in observing radiographic changes. It may be anywhere from several months to several years after his last dive that lesions are positively identified in a diver. Thus, if a man has had more than one hyperbaric exposure, no particular occasion can be singled out as responsible for initiating the disease process, unlike the case of a bend. It is not even known whether the correlation between the incidence of bone lesions and the number of exposures (MRC, 1966) is attributable to a cumulative effect of compressed air or the statistical chances of a single event occurring, i.e. the more times anyone takes the risk, the more likely he is to get caught. The second viewpoint (i.e. 'Russian roulette') would be favoured by the observation that of five non-diving submariners who performed a successful escape from the Royal Naval sub-

marine HMS *Poseidon* after it sank, three were found to have positive bone lesions when X-rayed ten years later (James, 1945). A single exposure to compressed air would appear sufficient to initiate the disease (Swain, 1942). On the other hand, the cumulative stand is favoured slightly by the observation that the incidence of bone necrosis was higher in tunnel workers on eight-hour shifts (18%) than in those who usually spent less than four hours in compressed air (11%) in the same tunnel but the numbers are not satistically significant (MRC, 1966). The increasing incidence with the number of exposures may be responsible for the apparent increase found in susceptibility with age (McCallum *et al.*, 1976), assuming that older men have spent more time working in compressed air.

The incidence increases not only with the number of exposures as already described but also with the exposure pressure. This is shown clearly by MRC (1966) statistics of tunnel workers where there is a positive correlation between the number of radiographically identifiable bone lesions and the maximum pressure of air in which each man has worked at some time in his career. The incidence seems to rise quite steeply on reaching 30 psi (67 fsw). In divers, the same trend seems to occur, although the smaller numbers involved make it harder to reach statistical significance. Royal Naval data collected by Elliott and Harrison (1971) indicate that few bone lesions, if any, occur in divers who have not exceeded 185 fsw upon air. However, two cases of disabling osteonecrosis have recently come to the attention of this author in divers who were engaged for a year or so on repetitive air diving to 80 fsw. It is very difficult to tell whether bone lesions can be caused by heliox exposures, since all caisson workers breathe air and all divers start their careers by diving on air.

Sites

Lesions occur predominantly in the head of the humerus and both ends of the femur (fig. 69); although there is some indication that the femoral head is less prone to the disease in divers (McCallum *et al.*, 1976). A feature of

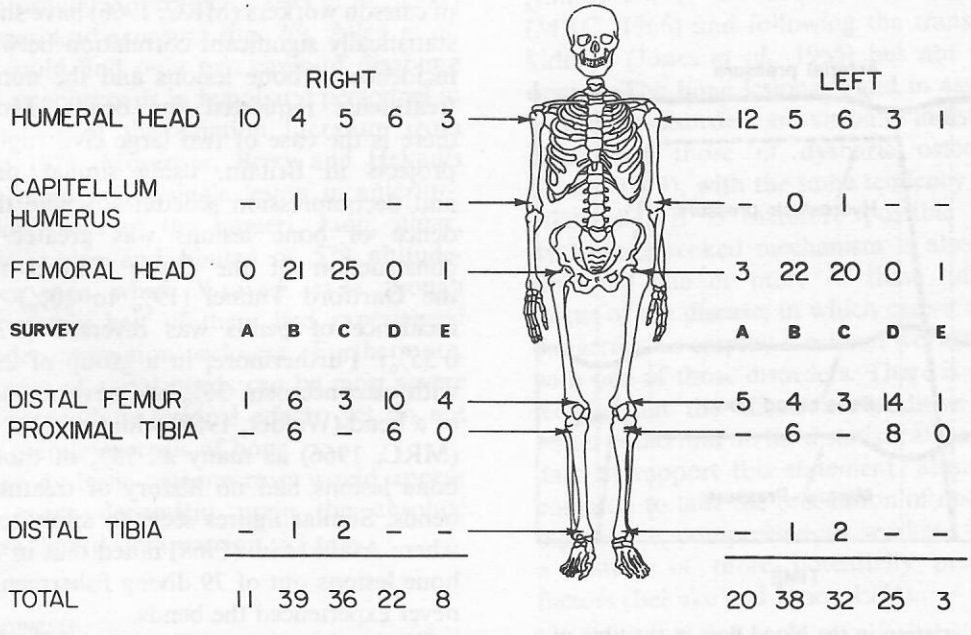

Fig. 69 A summary of the distribution of bone lesions found in five surveys: A: commercial divers (Fagan *et al.*, 1974), B: alcoholic patients (Jones, 1974), C: patients with hypercortisonism (Jones, 1974), D: naval divers (Harrison, 1974) and E: doubtful cases in naval divers (Harrison, 1974)

their distribution is the remarkable symmetry, unlike decompression sickness where bends occur predominantly in those limbs selectively exercised (p. 45). Not only does this occur overall but about half of the lesions detected occur bilaterally.

The lesions often follow no particular vascular distribution but those in the shaft tend to follow the contour of the bone, while those at the ends sometimes coincide with the old epiphyseal–metaphyseal plate (MRC, 1966). The general radiographic and microscopic picture seems to be compatible with post-fracture avascular osteonecrosis. Thus the mechanisms proposed are essentially aimed at explaining osseous ischaemia. However, the ischaemic episode would need to persist for at least 10–12 hours to initiate aseptic necrosis (Jones *et al.*, 1974). This rules out the transient changes in bone blood flow and intramedullary pressure induced directly by compression and decompression (fig. 70) as responsible for the dysbaric induction of the disease, infarction mechanisms providing more permanent means of locally interrupting the circulation. This suggests the same set of infarcting agents discussed in Chapter 3 in connection with the aetiology of decompression sickness. However, before passing on to mechanisms which assume an ischaemic episode in the pathogenesis of dysbaric osteonecrosis, it should be pointed out that death of the cells (osteocytes) is one of the few ways in which bone can manifest a physiological insult.

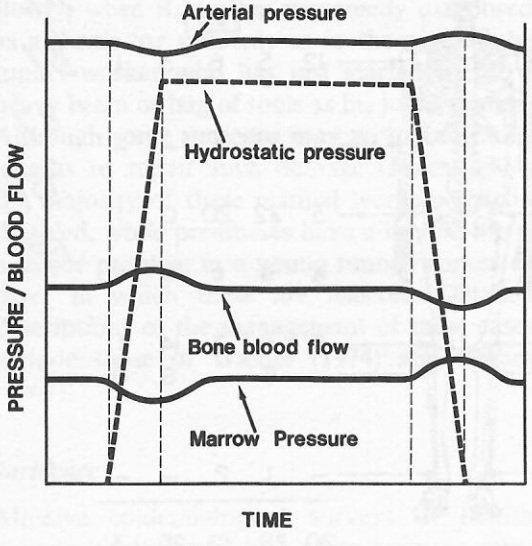

Fig. 70 Variation in the blood flow in the tibia of a dog and in the intramedullary pressure during the various phases of an exposure to compressed air at 45 p.s.i. (100′). Data from Harrelson and Hills (1970) and Hills and Straley (1972)

Comparison with the bends

If the same infarcting agents are causing both bends and bone lesions, then there should be a close correlation between the incidences of the two diseases. Moreover, this should also occur if bends were caused by extravascular gas as indicated in Chapter 3, since the decompressions depositing more gas in one site should also result in more bubbles in other sites including blood and hence more circulating emboli or their products of blood degradation or lipid release.

However, this does not appear to be the case in practice, where surveys of large numbers of caisson workers (MRC, 1966) have shown no statistically significant correlation between the incidence of bone lesions and the number of treatments requested for bends. Moreover, there is the case of two large civil engineering projects in Britain, using similar pressures and decompression schedules, where the incidence of bone lesions was greater in the construction of the Clyde Tunnel than in the Dartford Tunnel (19% to 10%) yet the incidence of bends was reversed (0·31% to 0·55%). Furthermore, in a group of 290 men with osteonecrosis, 36% had never complained of a bend (Walder, 1969) while in other groups (MRC, 1966) as many as 55% of those with bone lesions had no history of treatment for bends. Similar figures seem to apply to divers where Asahi *et al.* (1968) noted that in 15 with bone lesions out of 79 diving fishermen, 8 had never experienced the bends.

The only data indicating a correlation between bends and bone lesions has been presented by Elliott and Harrison (1970) on a relatively small number of Royal Naval

divers—a survey updated in many later papers by Elliott. However, taking the incidence of bone lesions in these men and their histories of treatments for decompression sickness from those data, both would appear to show more significant correlations with participation in 'experimental diving'. Moreover, if the divers are divided into those who have been engaged in 'experimental diving' and those who have not, then there is no correlation between bends and bone lesions in either group. Hence this could be another trap for the unwary; rather like attributing coronary artery disease to television because the incidence of this disease shows a very significant statistical correlation with the number of T.V. sets. These were shown not to be causally related but to be the result of a third factor (affluence) just as bends and bone lesions could result from experimental diving rather than from some common mechanism.

Another significant factor is the virtual absence of aseptic osteonecrosis in aviators, even though measurements of changes in general physiological parameters of bone, such as intramedullary pressure, show similar responses to both simulated altitude (Kalser *et al.*, 1951) and hyperbaric exposure (fig. 70). Allen *et al.* (1974) could find only two cases of disabling aseptic osteonecrosis in hypobaric personnel in their review of the aviation literature from 1945 to 1971. Moreover, Berry and Hekhuis (1960) found not a single lesion in anterior–posterior views of the humeri, radii, ulnae, femorae, tibiae and fibulae of 579 altitude-chamber men when X-rayed, even though approximately half of them had experienced acute decompression sickness. Furthermore, some cases of aerial bends can be most severe and even produce residual effects, yet do not induce aseptic necrosis of bone.

Hence dysbaric osteonecrosis would appear to be more dependent upon the absolute pressure than decompression sickness.

Pathogenesis

Despite the foregoing indications that bends and bone lesions are not causally related, most mechanisms which have been proposed for dysbaric osteonecrosis reflect those already put forward for decompression sickness, most involving vascular occlusion as described in Chapter 3. However, there is now a big difference in so far as it is not known whether recompression rapidly restores blood flow in a hypothetically occluded bone in the same way that it reverses limb pain. Hence lipid emboli and the other incompressible infarcting particles, particularly those produced by blood degradation, cannot be dismissed as the primary insult as readily as for decompression sickness.

Moreover, many of these are likely to be produced by the other disease conditions which tend to occur simultaneously with 'idiopathic' aseptic osteonecrosis, their accompanying blood disorders being succinctly described by Boettcher (1974). These predisposing factors include alcoholism (Axhausen, 1928; Vignon *et al.*, 1960), corticosteroid therapy (Pietrogrande and Mastromarino, 1957), sickle cell anaemia (Diggs, *et al.*, 1937; Chung and Ralston, 1969), rheumatoid arthritis and gout (Mauvoisin *et al.*, 1955), gouty arthritis (McCollum *et al.*, 1971), pancreatitis (Immelman *et al.*, 1964), Gaucher's disease (MRC, 1966) and following the transplant of kidneys (Jones *et al.*, 1965) but not of other organs. The bone lesions found in association with these disorders are virtually indistinguishable from those of dysbaric osteonecrosis (Jones, 1974), with the same tendency to occur bilaterally. It is therefore possible that the dysbaric-provoked mechanism is also responsible for one or more of these 'idiopathic' forms of the disease, in which case it would be dangerous to employ a caisson worker or diver with one of those disorders. There is a general feeling that the effects are additive but this writer could find no hard statistically significant data to support this statement; although it is common to take the precaution of not employing men as compressed-air workers who have a history of those potentially predisposing factors (Behnke and Jones, 1974).

Mechanisms: remotely generated insult

The assumption that aseptic necrosis of bone

is a result of inadequate decompression dominates the mechanisms which have been proposed so far, despite the lack of statistical correlation and consequently these were the first to be proposed in a list which includes:

(1) *Gas emboli*: Bubbles have been implicated in the pathogenesis of dysbaric osteonecrosis since the first demonstration of bone lesions in compressed-air workers (Bornstein and Plate, 1911). Occlusion of nutrient arteries by bubbles is a theme reiterated by many later workers and provides a simple concept still vigorously defended (Smith, 1974). One of the major pieces of evidence is the presence of large numbers of intravascular bubbles known to occur during many a bends-free decompression (p. 146). However, these gas emboli detected in *venous* blood would need to reach the arterial system to cause vascular occlusion and raises the old question of the effectiveness of the lung as a bubble trap (p. 66). It is also difficult to envisage bubbles randomly entering the nutrient arteries to bones causing such extensive areas of necrosis as Bornstein and Plate found without lodging in other organs where they would soon become manifest.

(2) *Extravascular gas*: This line of reasoning led Kahlstrom *et al.* (1939) to include extravascular gas as a means of obstructing bone blood flow. The large volume of nitrogen deposited from fatty marrow in which it is so soluble might press upon blood vessels tending to close them. This would certainly explain the magnitude of the lesion, bilateral symmetry and involvement of the humerus and femur where the fat content of the marrow is high (Rozsahegyi, 1956). Occlusion of blood vessels by extravascular gas would be more likely when it is mechanically 'contained' in a structure as rigid as bone and where, according to Nelson *et al.* (1960), vessel walls are particularly thin. The hypothesis is also highly compatible with the concept of perivascular 'cuffs' of fluid proposed by Hills and Straley (1972) to explain the opposing trends found in intramedullary pressure and bone blood flow on hyperbaric exposure (fig. 70) and on switching to and from anaesthetic gases. However, if the gas phase is responsible, a better correlation of bone lesions with bends would be expected and either intravascular or extravascular bubbles would need to persist for 10–12 hours to initiate necrosis.

(3) *Fat emboli*: Considerations of this factor has led Jones *et al.* (1974) to propose that dysbaric osteonecrosis is caused by infarction by lipid emboli whose impaction into the vascular bed would cause more than a transient reduction in blood flow. It is well known that fat emboli are produced by decompression (p. 55) while disruption of femoral marrow was thought to be the source (Clay, 1963). However, such fatty droplets deposited into the marrow circulation would need to occlude the venous outlet or, once again, traverse the lungs to reach the arterial system. Jones makes the major point that bubbles could cause the liver to release a shower of lipid emboli in the same manner that *alcohol* can provoke a fatty liver (Lynch *et al.*, 1959; Kimble, 1961). Thus aseptic osteonecrosis induced by decompression and by alcohol would have a largely common aetiology. However, if fat were a major factor, one would expect the incidence of bone lesions to vary with obesity but unlike decompression sickness (p. 41), such a correlation is missing (MRC, 1971). Unfortunately, by this hypothesis, it is also difficult to explain the apparent absence of lipid infarction of other organs and the failure to find bone lesions caused by other disease processes known to produce lipid emboli (McCallum, 1975) but, once again, these would need to reach the arterial system. However, there is the interesting case reported by Bühlmann (1974) where, at the autopsy of a subject who died six days after a simulated dive, diffuse fat embolization was revealed—not only of lungs but also of brain, heart, kidneys and the muscular system. The source of these emboli was a region of extensive haemorrhage in the marrow of the distal third of the left femur.

(4) *Blood clots*: The need for emboli deposited from other organs to reach the arterial system is largely avoided in the next type of mechanism related to the many blood disorders which can

occur during decompression. The debris can form into various potential infarcting agents or the general sludging can reduce the circulation to inadequate levels, particularly in organs such as bone which have few means, if any, of signalling ischaemia let alone responding to such feed-back by adjusting vasomotor tone. Potential infarcting agents include Swindle's red cell agglutinates proposed as a mechanism for decompression sickness by End (p. 49) and the microthrombi of platelets and red cell aggregates (Philp *et al.*, 1971). However, this mechanism suffers from the same criticism of other infarction hypotheses that it is difficult to explain the symmetry of dysbaric osteonecrosis, the absence of infarction of other organs and the failure of most other disease conditions producing those disorders to cause osteonecrosis.

(5) *Increased blood viscosity*: The increase in blood viscosity produced by decompression (Guest *et al.*, 1974) has led these authors to suggest this as a source of the ischaemic episode initiating the necrosis. The relative inability of the vasculature to respond to the higher resistance to flow of this sludged blood would therefore make bone a prime target but it is difficult to know whether the flow reduction would be large enough and last long enough. The viscosity increase is attributable to the known haemoconcentration on decompression (p. 51) but Guest *et al.* do not specify where the water goes or what moves it, a large proportion apparently going to the lungs. One possible driving force is osmosis induced by the higher gas concentration in tissue during that phase of the dive (p. 213) but the tendency for such shifts to persist for long periods (Hong *et al.*, 1976) indicates that the true explanation is likely to be physiological rather than physical.

Time course

However, in all of the mechanisms proposed so far, the ischaemic episode would need to occur at the time of decompression or within a short period thereafter, the longest delay recorded of any circulation-related phenomenon being three days for the drop in platelet level and rise in creatine phosphokinase (Martin and Nichols, 1972). Thus the time course of dysbaric osteonecrosis would seem altogether too long since, after the ischaemic episode, aseptic necrosis should proceed just as it would in the same bone post-fracture and become radiographically identifiable several weeks and not several months or even years after the last exposure (the minimum period is about $3\frac{1}{2}$ months—Walder, 1974). Although this is a very important point in differentiating between mechanisms, this statement is made from a collection of published comments (e.g. MRC, 1966) and discussions with radiologists but the clinical evidence is still rather fuzzy, due largely to the risk involved in taking long bone X-rays in men any more frequently than once a year. There is the odd case quoted in the literature where necrosis of the femur could not be identified until $9\frac{1}{2}$ months post-fracture, (Stewart, 1933) but these seem to be the exceptions rather than the rule. Hence it would appear that either dysbaric osteonecrosis is not ischaemically mediated or there is a long induction period in producing the ischaemia, in which case it is more likely to be induced locally.

Mechanisms: local insult

This line of argument has tended to focus more attention on more subtle forms of insult likely to be generated within bone itself and has provided the following mechanisms to continue the original list:

(6) *Oxidation of collagen*: Sobell (1971) has shown changes in the collagen of rats exposed to oxygen partial pressures in excess of normal and has gone on to point out how such changes could influence the deposition of hydroxyapatite upon the collagen matrix in forming bone, implying that this could be a factor in dysbaric osteonecrosis. There is little doubt that mineralization is very sensitive to a number of factors, an excellent introduction to this complex process being found in the monograph written by Neuman and Neuman (1958). One of the

controversies in this field concerns the provision of nuclei for the regulated precipitation of mineral from solution in which it is supersaturated under normal conditions—even in plasma (Strates and Neuman, 1958). Glimcher and Krane (1968) review the cases for homogeneous nucleation (p. 78) versus heterogeneous nucleation where the collagen provides the sites for the deposition of hydroxyapatite as needed, their evidence tending to favour the second approach. All of this refers to air breathing at normal atmospheric pressure, so that it is quite conceivable that a change in the molecular structure of collagen, such as cross-linking adjacent polymer chains by oxygen, could totally disorganize the mineralization process. Since this is very slow, it could take months or years for the results of incorrectly seeded crystals to become manifest. However, if oxygen were the agent responsible for dysbaric osteonecrosis, one would expect to find aseptic necrosis of bone in subjects who had received oxygen therapy, since their exposure to oxygen even at normal pressure is appreciably greater than needed to provoke the collagen changes seen in Sobell's rats.

(7) *Carbon dioxide*: Another possible insult to the normal biochemical processes in bone could occur if the pH were reduced by exogenous means. Bone resorption occurs if the pH is reduced by the generation of lactate and citrate ions within the osteocyte among other factors (Raisz, 1970). Certainly a fall in pH is associated with bone resorption (Neuman and Neuman, 1957) just as a piece of bone demineralizes when dropped into acid *in vitro* (Deiss, 1974). Hence it is tempting to speculate that an elevated level of carbon dioxide might do the same. Lung disorders are occasionally cited as associated with 'idiopathic' aseptic osteonecrosis (Davidson, 1964). The diver or tunnel worker who proves to be a carbon dioxide retainer under pressure (p. 206) may be prone to this disease. This could not only explain the absence of bone lesions in aviators but the high incidence in the five submariners who did not escape from HMS *Poseidon* until several hours after the accident (James, 1945), during which time they would probably have become hypercapnic. This mechanism could also offer a possible explanation for the variation in the incidence of bone lesions between tunnel projects, carbon dioxide released from the earth of the diggings being something characteristic of that particular site.

(8) *Gas-induced osmosis*: The mineralization process is highly regulated under normal conditions and particularly sensitive to water content (Neuman and Neuman, 1958) so that any fluid shift could disorganize this finely balanced process. One means of effecting this shift is by osmosis induced by the transient imbalance of inert gases as they are taken up or eliminated by bone during compression or the rapid initial phase of decompression (Hills, 1970e, 1972a). Rapid compression can cause fluid shifts *around* bone as evidenced by 'dry joints' (p. 206), while articular cartilage has been shown to be an effective osmotic membrane for nitrogen in solution (Hills, 1971e). These shifts could also occur *within* bone, in which case compression should produce the same effect as switching the inert gas to one which is more osmotically potent (nitrous oxide), while the return to normal air breathing should correspond to decompression. These are in agreement with recordings of two of the simplest parameters to monitor—bone blood flow and intramedullary pressure (Harrelson and Hills, 1970; Hills and Straley, 1972).

Hills (1970e) goes on to speculate that one way by which intra-osseous fluid shifts could induce aseptic necrosis would arise if the dissolved minerals did not permeate the osmotically active membrane as readily as the displaced water. Their normal supersaturation would then be increased to a degree at which they would seed spontaneously, as described for bubbles (p. 78), thus forming *homogeneous* nuclei rather than waiting for a heterogeneous site to occur. Hence the regulation of mineralization would break down and the nuclei formed would continue to grow under the normal state of supersaturation, even without further diving, eventually to produce crystals in the undesirable places where they could occlude

blood vessels or cause other embarrassment to the osteocytes. It is necessary to remove no more than 5% of water from normal plasma to initiate spontaneous mineral deposition (Hills, 1973a) whereas the shift needed to initiate crystallization may be less on days when a diver's diet has elevated his natural level of mineral supersaturation.

This hypothesis is not only compatible with the time course of dysbaric osteonecrosis but with its bilateral incidence and the tendency to occur idiopathically after kidney transplant (i.e. dehydration concentrating minerals) and with excessive alcohol—a potent osmotic agent, mild diuretic and an agent for 'salting out' dissolved minerals. The maximum rate of pressure change is another factor unique to each tunnel project, depending upon the size of the lock and its valves, compression rates estimated for six U.K. tunnels lying in the same order as the incidence of osteonecrosis but not of the bends rate.

In addition to the foregoing mechanisms, McCallum (1975) also suggests that nitrogen could prove toxic to bone cells but the biochemical evidence on which this possibility is based (Deiss *et al.*, 1962) actually refers to a means by which hypoxia can inhibit the biosynthesis of collagen.

Prevention

It must be remembered that each of the eight possible mechanisms listed above is hypothetical and none may prove to be correct in the final analysis. If the primary cause is bubbles (1 and 2), or the results of their presence in the form of fat emboli (3) or microthrombi (4), then the same means of preventing bends should also be effective in preventing dysbaric osteonecrosis, viz. more adequate decompression. However, appreciable increases in total decompression time introduced in the tunnel projects carefully followed on large numbers of men by the MRC (1971) have failed to show any improvement in the incidence of dysbaric osteonecrosis. Enough time has now elapsed for any improvement to be detected. These changes have been more effective in reducing gas separation and its effects, since the incidence of bends has been reduced appreciably; so there is good reason to look beyond the popular mechanisms (1 to 4) for the cause. The time course for the disease is also difficult to interpret by these infarction approaches and by the rheological mechanism (5). This and the *local* mechanisms (6, 7 and 8) can all explain bilateral symmetry, the absence of bone lesions in aviators, while all of these except the oxygen hypothesis (6) are compatible with potentiation of the disease by alcohol.

Of the remaining mechanisms to which there are no obvious incompatibilities with the principal features of the disease, the following implications can be drawn.

(a) The carbon dioxide mechanism (7), if correct, would emphasize clean air and good ventilation and switching to heliox where possible to minimize carbon dioxide retention. Modification of the decompression would have no effect.

(b) A mechanism based on gas-induced osmosis, either directly (8) or indirectly (5), would implicate rapid change of pressure as the cause, whether undertaken during the first phase of decompression or during compression (8). In this connection it is interesting to see bone lesions arising in submariners undergoing escape training (Elliott, 1974) where compression and decompression are both very rapid and carbon dioxide build-up cannot be invoked; while slow compression (20 ft/min) has yielded a low incidence of bone necrosis (Sealey, 1974) but for quite moderate exposures. Rapid compression has again been implicated in recent studies on small animals (Chryssanthou, 1975) and adds support for the suggestion of *compression* tables (Hills, 1970e, 1972a).

Hence, if dysbaric osteonecrosis is not simply another symptom of inadequate decompression as most believe it to be, then the answer to its prevention could lie in keeping body carbon dioxide to normal levels, or in changing pressure much more slowly than usual, either

in compressing or in decompressing to the first stop. However, none of these factors may hold the answer; while the final outcome could well prove that the disease can be initiated by several mechanisms.

Other Diving Limitations

Mechanical factors such as 'the squeeze' 'burst lung' (p. 13) and certain pulmonary aspects have already been discussed. The remaining factors, which include inert gas narcosis, the high-pressure nervous syndrome and hyperbaric arthralgia, can limit the rate of compression, ease of breathing and speech and therefore add constraints to the use of inert gases; although these are mostly minor by comparison with decompression sickness. Oxygen toxicity limits the substitution of oxygen for inert gas, while pressure *per se* might one day prove a limit to the exposure depth itself.

Inert gas narcosis

Nitrogen narcosis closely resembles alcoholic intoxication, an effect first noted by Junod in 1835 but not attributed to the nitrogen component of air until a century later (Behnke *et al.*, 1935b). The impairment of mental function by the inert gas can range from the euphoria and loquacity often noticed in caisson workers at $5\frac{1}{2}$ ATA (Hill and McLeod, 1903) to amnesia, dangerous hyperconfidence and difficulty in decision making with lapses in consciousness being observed in some divers at 330 fsw (11 ATA). Hill and Phillips (1932) aptly describe the whole process as 'a slowing of the process of cerebration'. The allusion to alcoholic intoxication extends beyond these similarities in symptomatology. It includes adaptation (Adolfson and Muren, 1965) and susceptibility, individuals more prone to one being more prone to the other to the extent that a 300-foot air exposure has about the same effect in the same man as consuming 'ten beers' at the surface. Unfortunately, there is no evidence that acclimatization to one protects against the other, or diver training would be most popular!

Individual susceptibility is determined, in part, by emotional stability (Cousteau, 1953) while the narcosis can be potentiated by carbon dioxide retention (Shilling and Willgrube, 1937; Bean, 1950; Seusing and Drube, 1960) and to a lesser extent by hyperoxia (Hesser, 1963) and hypoxia (Albano *et al.*, 1962) which leads to many of the same symptoms. Hence manifestations of one can easily be incorrectly diagnosed for the other. Denser inert gases tend to be more narcotic, enabling smaller partial pressures to induce the same degree of incapacity as in proceeding to the gaseous anaesthetics (see Table 15). This comparison implies that gaseous anaesthesia is an extension of inert gas narcosis and indeed the evidence points to an exactly analogous mechanism underlying both (Bennett and Glass, 1961).

This mechanism has attracted theoretical speculation for over a century and still remains an open issue. It seems as though the answer lies at the molecular level, a superb review of the underlying physical and physico-chemical factors having been compiled by Miller and Smith (1973).

Mechanisms which have been proposed include the retention of carbon dioxide (Bean, 1950), clathrate formation (Pauling, 1961), 'iceberg' formation (Miller, 1961) and various 'bonding' mechanisms (Featherstone *et al.*,

Table 15 Equi-narcotic partial pressures of inert gases

Gas	Equi-narcotic* partial pressure (atm)
He	(190)
Ne	110
H_2	85
N_2	35
A	24
CF_4	19
SF_6	6·9
Kr	3·9
Xe	1·1

*Data taken from Miller *et al.* (1967).

1961; Schoenborn *et al.*, 1965); while numerous electro-physiological hypotheses have also been proposed. Most of these have either a physical or biochemical basis and involve the concept of a block of ion exchange across a membrane. The transient component of narcosis has been attributed to gas-induced osmosis (Hills, 1971b) but the major effect of inert gases does not ameliorate with time to any appreciable extent (Case and Haldane, 1941). However, the most interesting mechanism to be proposed surrounds the observation (p. 208) that pressure *per se* tends to reverse the narcotic effects of gases, not only in tadpoles but also in newts and mice (Lever *et al.*, 1971b). Moreover, a loss of righting reflex induced by 34 ATS partial pressure of nitrogen was restored by raising the absolute pressure to 140 ATA by the addition of helium. This led the Oxford group to explain the antagonistic action of pressure on certain anaesthetics by the recompression of membranes expanded by the gases taken up in solution, the volume change dislocating electrical pathways (Lever *et al.*, 1971b). This concept has been extended to quantify the anaesthetic potency of a gas on the basis of the 'free volume' it forms in the cell membrane (Stern and Frisch, 1973). What is therefore of particular significance is the fact that, unlike other gases, helium tends to *reduce* solvent volume when it dissolves. Helium does not induce narcosis.

Thus the narcotic effect of nitrogen can always be avoided if its partial pressure is reduced by replacing it with helium, either in part or as a whole. However, the diving outfit is then faced with the additional cost of providing an expensive inert gas, so that air is preferred whenever possible. Minimum air pressures quoted for the onset of nitrogen narcosis in men vary from 6·4 ATA (180 fsw) (Miles and Mackay, 1959) to 2–3 ATA (Poulton *et al.*, 1964) but the value of 4 ATA (100 fsw) originally quoted by Behnke *et al.* (1935b) is still the best accepted. It is now general practice to substitute helium for at least 60% of the nitrogen when diving deeper than 200–250 feet.

Mixtures of helium, nitrogen and oxygen are economical for chamber systems where the exhaust gases are reclaimed, since these just need 'topping up' with helium and oxygen. The retention of some nitrogen in these 'trimixes' has the advantage of increasing the intelligibility of speech by improving voice quality from the 'Donald Duck' tones heard in simple helium : oxygen breathing mixtures. Hence inert gas narcosis need present no problem if the nitrogen partial pressure is not permitted to exceed 3–4 ATS.

Ventilation at pressure

Another factor influencing the choice of inert gases, or the blend selected for a particular dive, is the ability of the chest muscles and diaphragm to ventilate the lungs adequately at the 'bottom' depth. Since the resistance to gas flow in the airways is largely density dependent, the work of breathing would increase substantially as a subject is compressed in air if he were to maintain the same tidal fluctuations in lung volume.

One of the best indices of a diver's respiratory capability is provided by the maximum voluntary ventilation (MVV), i.e. the most a man can breathe over a short period (around 15 sec) when consciously expending maximum effort in doing so. Hence it is most significant that the MVV can decrease from over 200 $l\,min^{-1}$ (ATPS) on air at the surface to less than 80 $l\,min^{-1}$ (ATPS) at 200 fsw (Maio and Farhi, 1967), following a $1/\sqrt{(\text{density})}$ relationship quite closely (Wood, 1963).

However, when the diver is not consciously controlling his frequency of breathing and tidal volume, he is then dependent upon his neurogenic and humoral control mechanism to compensate for the potential fall in ventilation which this increased work load tends to impose. In practice, such a fall leads to carbon dioxide retention which is then 'sensed' by the chemoreceptors of the body to increase respiratory stimuli and result in a positive ventilatory response of the chest and diaphragm muscles. This response does not compensate totally but as Cain and Otis (1949) point out, the body tends to adopt a compromise between

allowing the carbon dioxide to rise and expending more effort in respiration. However, not all individuals reach the same position of compromise, some letting their arterial P_{CO_2} rise more than indicated by typical values of 41 rising to 45 mm Hg in compressing from 1 to 4 ATA on air (Saltzman *et al.*, 1971). These 'carbon dioxide retainers' have become acclimatized to high P_{CO_2} according to Schaefer (1969) but such abnormalities do present a real risk in that those individuals may pass unconscious on deeper dives.

The fear of excessive carbon dioxide retention is another reason for switching from air to helium : oxygen mixes shallower than one might feel inclined on the basis of nitrogen narcosis alone, some diving outfits starting to substitute helium for nitrogen as shallow as 150 fsw. The switch from nitrogen to helium greatly eases the work of respiration which is dependent upon gas density alone (Maio and Farhi, 1967). This seven-fold theoretical advantage of helium over nitrogen has been demonstrated in a report that carbon dioxide retention and the MVV was approximately the same with 94·5% helium at 20 ATA as for air at 2 ATA (Hamilton *et al.*, 1966; Hamilton and Langley, 1971). Where the cost of helium is a prohibitive factor, this writer has observed air diving performed perfectly adequately at 300 fsw but with divers maintained particularly well acclimatized to that environment (LeMessurier and Hills, 1965).

However, when ventilation becomes inadequate, the symptoms are primarily those of hypercapnia sometimes accompanied by hypoxia (see p. 220).

Hypercapnia

Carbon dioxide can be retained in the body not only by virtue of inadequate ventilation but from external causes such as the failure of a scrubber system to absorb sufficient carbon dioxide or from contamination of a gas supply. Carbon dioxide accumulation in tissues leads to acidosis, the detailed physiology having been particularly well reviewed by Schaefer (1965).

Unlike oxygen, the acidic nature of carbon dioxide enables any change in the blood tension of this gas to be detected very readily by the chemoreceptors in the body. Addition of 0·02 ATA carbon dioxide to the breathing mix is sufficient to stimulate the respiratory centre causing perceptible hyperventilation until, at 0·05 ATA, it is greatly increased to the point where it can cause distracting discomfort unless alleviated within a few minutes. At an inspired P_{CO_2} around 0·10 ATA, carbon dioxide can then start to have a depressant rather than a stimulating effect upon the central nervous system. This can start with drowsiness, mental confusion, lack of visual discrimination and can lead to dizziness, nausea, headache—easily confused with symptoms of hypoxia (p. 220). Kept at those levels for 10–60 min, or exposed to an even higher P_{CO_2}, the diver can pass unconscious, sometimes displaying generalized convulsions which can easily be mistaken for neurologic oxygen toxicity (p. 217). The early warning signs may go unrecognized if the diver is already hyperventilating from hard work when he runs the risk of 'blacking out'. He is easily revived by return to a subtoxic mixture if his distress is noticed in time.

Hyperbaric arthralgia and barotrauma

The next set of limitations are imposed by the rate of compression. Most individuals who have difficulty in admitting gas to their middle ear via the Eustachian tube, i.e. in 'clearing their ears' during descent, simply do not become divers, since barotrauma can be very painful. However, there is the odd occasion when it is more difficult even in the professionals and the compression must be slowed or stopped until the subject can equalize pressures between the surroundings and his various natural gas cavities.

This leaves two other effects of rapid compression; hyperbaric arthralgia and—in going to extreme depths—various neurological disorders known collectively as the high-pressure nervous syndrome (HPNS).

The 'popping' of joints and a pain similar to that experienced in arthritis can be induced

by rapid compression. This was noted by Cousteau in the Conshelf III dives and reported by Hamilton *et al.* (1966) who attributed the effect to a 'lack of joint juice', while many divers describe similar pains on much shallower dives. The U.S. Navy often observe this hyperbaric arthralgia in routine dives to 300 fsw (Fenn, 1969) but the pain is minimized if more time is taken to descend. Similar dependence on the compression rate has also been reported by Krasberg (1966) who found that a decreased oxygen tension also ameliorates the joint pains. This is interesting since such pains have been reported with exposure to hyperbaric oxygen alone.

Many mechanisms can be derived to explain hyperbaric arthralgia but the simplest is based upon an efflux of fluid from the joint capsule induced osmotically by gases; both by transient gradients of inert gases and by permanent gradients of the metabolic gases (see p. 217). Whatever the true aetiology, it can be minimized simply by taking more time to compress.

High-pressure nervous syndrome

When a diver is rapidly compressed, say at 100 fsw per min, to 500 fsw, he will probably experience a coarse tremor and other neurological disorders which Brauer (1968) has most appropriately termed the high-pressure nervous syndrome (HPNS). This is also produced if one applies more hydrostatic pressure than is needed to reverse narcosis (Miller *et al.*, 1967). The coarse tremors constitute a considerable nuisance to the diver going to extreme depths since, even at 500 fsw, he may have to wait for 5–15 min before he can start to weld or to do any other manual task requiring an appreciable degree of precision. This means that he then incurs a disproportionately large penalty in decompression time.

There are not only motor and intellectual decrements in performance but, at depths of 600–800 fsw, these are accompanied by dizziness, nausea and vomiting. Although HPNS can be avoided by slowing the compression on heliox, the rate needs to be reduced enormously as pressures exceed 1000 fsw, times of the order of 2–4 days often being needed to reach depths of 1300–1600 fsw; while Comex took 7–8 days in reaching 2001 fsw in one chamber trial (Fructus and Charpy, 1972).

Current techniques involve the use of a narcotic to suppress the hyperexcitability of the nervous system otherwise manifested by the HPNS. Thus Comex have pioneered the addition of nitrogen to the breathing mix (Vigreux, 1970); while Krasberg (1976) prefers to administer a little alcohol at depth, since this does not contribute to bubble formation later and can be cleared from the body in about the time it takes to decompress from those depths. Moreover, alcohol can be prescribed by anyone and comes in many forms most palatable to the diver!

The mechanism of the HPNS is certainly not obvious and has been discussed in recent reviews by Brauer (1975) and Hunter and Bennett (1974). However, those aspects which are independent of compression rate can be readily explained by the 'critical volume' concept as determined by pressure *per se* in the hypothesis derived by Paton, Miller and their associates at Oxford (see page 204). The aspects dependent upon compression rate are much harder to explain but Chouteau *et al.* (1971) have implicated gas-induced osmosis (p. 213); although it is difficult to envisage a molecule as small as helium possessing any significant osmotic potency.

From a practical standpoint, HPNS is no problem unless the dive requires an exceptional exposure and then it becomes a question of simply reducing compression rate or, if this is unacceptable, then using a narcotic to suppress the nervous system. There is then the choice between alcohol, as used so effectively by Krasberg, or nitrogen; but much experimentation with various trimixes is currently in progress. A particularly fast simulated descent and one enabling a diver to reach 1600 fsw *in a fit state to work*, has been achieved by Lambertsen and his associates at the University of Pennsylvania who rapidly compress to 1200 fsw in 2½ hours, wait at that depth for half-an-hour to let the HPNS subside and then proceed at 3 fsw per min (Peterson, 1976).

Summary

The blending of inert gases therefore becomes a compromise between the ventilatory and narcotic advantages of helium on the one hand and the ability of a little nitrogen to suppress any HPNS, together with the improved quality of speech imparted by nitrogen and its cheapness, on the other—not to mention the problems posed by helium in maintaining thermal comfort of the diver. However, all of the above problems can be avoided with the appropriate blend of gases for all but exceptional exposures. The same can be said of oxygen toxicity but the enormous benefits derived from substituting oxygen for inert gas in preventing or treating decompression sickness necessitates singling out this syndrome as one of particular importance to the designer of diving tables and hence one to be discussed in greater detail later in this chapter (p. 217).

Hyperbaric Phenomena

There are a number of physical and physiological phenomena which have been observed under hyperbaric conditions or have the potential for being troublesome under these conditions. These include pressure *per se*, counterdiffusion supersaturation, counterperfusion supersaturation, gas-induced osmosis, collision fission of bubbles, etc. In addition, there are a few techniques such as liquid breathing which have considerable potential for development as a means of prevention and treatment of decompression sickness.

Pressure per se

Hydrostatic pressure itself is unlikely to have any adverse effect on normal diving on the continental shelf (i.e. up to 30 ATA). Many biochemical processes are pressure dependent but need pressures of the order of 1000 ATA to be studied effectively; so that man's deepest exposure to data (61 ATA) hardly appears on most scales. A superb review of these biological phenomena has been compiled in a comprehensive volume published by Zimmerman (1970). Extreme pressure can change the viscosity of fluids, the conductivity of solutions and the rate of many biochemical reactions, while it also facilitates the transition from gel to sol. This phenomenon is very pertinent to the consistency of cytoplasm which can liquefy at pressures as high as several hundred ATA (Marsland, 1970), while denaturation of proteins can also occur. These and other basic biochemical and biophysical phenomenon are probably mediated through the volume change which is the only way that a tissue can 'know' that it is being compressed (Cattell, 1936).

At the physiological level, it is necessary to study either excised tissues held in fluid baths or whole creatures which are liquid-breathers to ensure that any effects observed cannot be attributed to changes in the concentrations of dissolved gases. Tadpoles show increased activity as the pressure is increased to 150 ATA but, above this, spasms and paralysis occur (Johnson and Flagler, 1950). Turning to liquid-breathing mammals, rapid compression elicited tremors and spasms in the limbs of mice over the range 50–80 ATA with tonic convulsions at higher pressures (Kylstra *et al.*, 1967).

At the micro-physiological level, pressure can change many of the properties of excitable membranes through numerous indirect routes which are the centre of much speculation. To take the neurophysiologists classical preparation, the squid giant axon, resting potential was unaffected and action potentials were prolonged at 300 ATA; while threshold current and potential showed the first reduction as low as 7 ATA until the nerve fired spontaneously on reaching 200 ATA (Spyropoulos, 1957). Pressure tends to enhance the action of local anaesthetics such as cocaine and to reverse the action of many general anaesthetics such as the narcotic gases (Spyropoulos, 1957; Roth *et al.*, 1975).

However, none of the effects of pressure *per se* seem to be appreciable below pressures corresponding to the depth of the continental shelf, and incidentally, those to which diving mammals have become acclimated. Thus hydrostatic pressure alone should have a minimal

effect, if any, for all normal diving—i.e. to depths less than 1000 fsw.

However, in order to study the effects of pressure *per se* in the mammalian system, or to gain the benefits of hydrostatic pressure divorced from gas uptake, it is necessary to employ liquid breathing.

Liquid breathing

In Chapter 5 it was seen how a fish avoids decompression sickness in the ocean because he ventilates his gills with an incompressible fluid, water, which is unsaturated by gas with respect to his ambient hydrostatic pressure. The same means of avoiding all of the undesirable aspects of gas uptake and decompression can be applied to man if he were to breathe a suitably oxygenated liquid. The feasibility of this technique has been extensively investigated by Kylstra (1968) who summarizes the results of many of his experiments keeping mice and dogs alive breathing normal physiological saline with a P_{O_2} of several atmospheres. Thus he has decompressed a mouse from 30 atmospheres to normal pressure in 3 seconds without any untoward effect of such a rapid decompression. Moreover, a human volunteer claimed that it did not feel noticeably different when one lung was ventilated with saline.

However, even assuming that the engineering back-up is totally reliable, liquid breathing must be regarded as somewhat of a novelty until two major limitations can be overcome.

The mammalian lung never evolved with the pumping capacity to ventilate the airways with such a dense and viscous fluid as water in the manner of the gill. Secondly, filling the space between pulmonary blood and the tidal regions of the lung with liquid greatly increases this diffusion barrier (Kylstra *et al.*, 1966) otherwise assumed to be negligible in the air-filled lung (see Table 1). Despite these problems, blood oxygenation can still be maintained by

(1) using a ventilating fluid in which oxygen is very soluble, such as the fluorocarbons (Clark and Gollan, 1966) and

(2) simply elevating the oxygen tension of the ventilating liquid until the driving force is sufficient to provide the necessary flux of oxygen into pulmonary blood however large the barrier, the only limitation being the hydrostatic pressure needed to keep it in solution.

While these techniques are fine for satisfying the moment-to-moment oxygen demands by the body, they do not circumvent the effects which reduced ventilation and an increased airway–blood barrier pose to the transfer of carbon dioxide in the reverse direction. From the discussion of hypercapnia (p. 206), it was seen how little the arterial P_{CO_2} may be allowed to rise, so there is little increase available in the driving force for carbon dioxide elimination. Moreover the solubility of carbon dioxide in fluorocarbon is no greater than it is in saline. At least in saline, buffers can be added to absorb carbon dioxide chemically, while the most popular of these, Tris-buffer or THAM, can also facilitate the diffusion of carbon dioxide (Schoenfisch *et al.*, 1975). That is, it can increase the diffusion coefficient (D) in addition to the effective solubility.

Recent advances in Kylstra's laboratory have led to the use of emulsions of fluorocarbon in Tris-buffered saline, so combining an oxygen carrier with a carbon dioxide absorber. To increase this absorption still further, 2N solutions of sodium hydroxide have been tried but to prevent such a caustic solution having contact with epithelium, the emulsion is inverted to present fluorocarbon as the continuous phase (Matthews and Kylstra, 1976). However, this might introduce wetting problems, since fluorocarbon has an appreciable contact angle with water (Hills, 1974c) and hence with aqueous tissue, which might result in difficulty in the change-over from air to the liquid ventilating medium. Many references are cited by the manufacturers of fluorocarbon to show that these liquids are essentially non-toxic in their carefully distilled form (Mediflor, 1975).

Despite the encouraging research in this direction, liquid-breathing must still be regarded as a novelty with respect to the prevention of decompression sickness. However, it offers a unique opportunity to *treat* decompression sickness under the well-controlled conditions

of the medical chamber where it does not matter unduly if a subject is disorientated by fluid in his sinus and middle ear cavities. It would enable enormous hydrostatic pressures to be applied to bubbles and so crush them when normal recompression had failed to alleviate symptoms. Moreover, it would avoid the major fear that, if recompression fails, then the problem is exacerbated by the additional inert gas which can be taken up by a gas-breathing subject during treatment.

Counterdiffusion supersaturation

Consider a gas diffusing from a source at a high tension (p_1) across a uniform medium to a sink at a lower tension (p_2). If p_1 and p_2 are maintained constant, the system will eventually reach a steady-state for which the gas distribution will be determined by the overall geometry in accordance with Fick's law (fig. 65a). Moreover, this gradation in tension from p_1 at the source to p_2 at the sink is the same for any inert gas (A) whatever its solubility and diffusivity. If a second gas (B) is now introduced and caused to diffuse in the opposite direction to A by maintaining its tension as p_1 at the sink for A and p_2 at the source for A, then B will have a tension distribution within the medium which will exactly reciprocate that of A. Thus the total tension of the two gases ($p_A + p_B$) will be the same at all points when the system has reached a steady state, amounting to the total ($p_1 + p_2$) in the gas phase on either side.

However, if the medium is not homogeneous, then this need no longer be true. Thus Graves *et al.* (1973) point out that if ($p_1 + p_2$) is the absolute pressure P in accordance with Dalton's law, there can now be points within that heterogeneous system where ($p_A + p_B$) can exceed P, i.e. where the counterdiffusion of A and B can lead to supersaturation. If the medium is now composed of two phases, one aqueous and the other lipid, with the source of a gas

p. 182

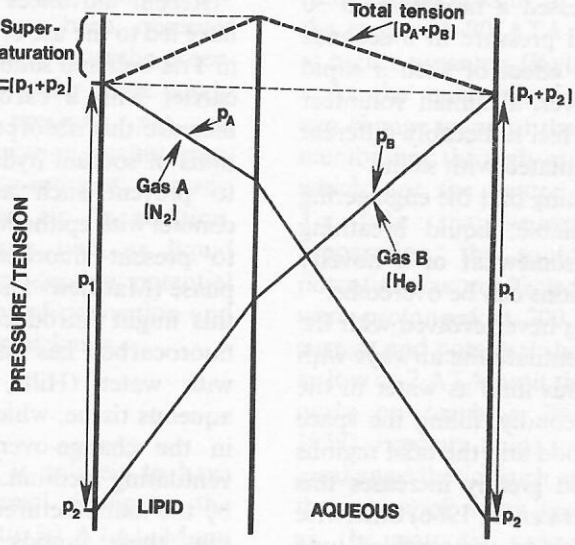

Fig. 71 Illustrating the principle of counterdiffusion supersaturation where a steady state has been reached for a gradient of ($p_1 - p_2$) for helium in one direction and nitrogen in the other. Note how the total tension at the aqueous–lipid interface exceeds the absolute pressure ($p_1 + p_2$) and represents the point of peak supersaturation. Redrawn from Graves *et al.* (1973)

relatively more permeable in fat (nitrogen) adjacent to fat and one relatively more permeable in water (helium) adjacent to water, then supersaturation will occur. This is depicted for the simple case of two flat layers of fat and water in fig. 71, the peak total tension occurring at the interface in this case. If the gases are switched, then there is a *minimum* total tension, or a peak unsaturation at the interface.

When the first system was tested experimentally, seeded bubbles were found to grow at the interface. The condition for supersaturation to occur is derived by Graves *et al.* as

$$S_f D_f / S'_f D'_f > S_a D_a / S'_a D'_a \qquad (65)$$

where S_f, S_a, D_f and D_a are the fat and aqueous solubilities and fat and aqueous diffusion coefficients for one gas; while S'_f, S'_a, D'_f and D'_a are those for the other gas diffusing in the opposite direction. Graves *et al.* point out that the height of the peak (fig. 71) is also influenced by the relative thicknesses of the two layers which, if optimal, could lead to supersaturation of the order of 30% of absolute pressure. Moreover, if it occurs at a lipid–aqueous interface, this is also an ideal site for nucleating bubbles (see p. 89).

Counterdiffusion in vivo

In the living animal there are never just two inert gases to be considered; there are also the superimposed effects of the metabolic gases which give rise to an inherent unsaturation (p. 239). Thus under normobaric conditions, it is difficult to envisage the inert gas peak generated by counterdiffusion exceeding this unsaturation to result in a net supersaturation. However, under hyperbaric conditions, especially with a reduced oxygen fraction in the breathing mix, the net supersaturation can become appreciable.

Hence cavitation induced by this form of supersaturation has been offered as an explanation for two hyperbaric phenomenon which occur in situations ideal for counterdiffusion. These are the hyperbaric urticaria observed by Blenkarn *et al.* (1971) in subjects breathing nitrogen : oxygen mixes in a chamber filled with heliox, later confirmed by Lambertsen (1975) who went on to higher pressures to show vestibular derangement. These observations are particularly interesting since one is indistinguishable from 'skin bends' (p. 31) and the other from 'vestibular bends' (p. 31) and yet both occurred at times when there had been *no decompression.*

The situation where the skin was exposed to helium while cutaneous blood was saturated with nitrogen would provide an ideal opportunity for counterdiffusion across the epithelium. It is not obvious where a suitably orientated lipid–aqueous bilayer occurs but, since lipid is present subcutaneously there could be supersaturation and hence cavitation without decompression. Thus Graves *et al.* have offered counterdiffusion supersaturation as an ingenious explanation for hyperbaric urticaria. Moreover Idicula *et al.* (1975) have actually demonstrated cutaneous gas in pigs under these conditions.

Graves *et al.* (1973) offer the same explanation for no-decompression vestibular derangement (Sundmaker, 1974) but there is no identification of the suitably orientated lipid–aqueous bilayer necessary for supersaturation. This bilayer is not necessary in alternative hypotheses which have been put forward for both the urticaria and the vestibular phenomenon—viz. those based upon gas-induced osmosis and counterperfusion supersaturation which would occur under the same circumstances. However, before discussing these alternative mechanisms, there is another more recent finding which has been attributed to counterdiffusion supersaturation. This is the continuous production of intravascular bubbles when the subject is exposed to heliox, yet breathing a mix of either nitrogen : oxygen or nitrous oxide : oxygen (Cunnington *et al.*, 1975). Once again it is difficult to delineate the relevant lipid–aqueous interface for the bubbles to be formed *in blood.* However, this objection has been avoided in a somewhat analogous mechanism for which Hills (1976a) has coined the phrase 'counterperfusion supersaturation'.

Counterperfusion supersaturation

Consider a region of tissue being perfused at a rate $\dot{Q}$ with blood saturated only with gas I at the ambient pressure (P). If this zone is surrounded by a diffusion barrier of area A and thickness x whose remote face is continuously flushed with another gas II also kept at ambient pressure, then Fick's law can be applied to give the flux of each gas by diffusion ($\dot{q}_1$ and $\dot{q}_2$) which must also equal the transport of each gas by perfusion for steady state to be attained (see fig. 72).

Thus for gas I

$$\dot{q}_1 = AD_1 S_1 (P - p_1)/x = \dot{Q} S'_1 p_1 \qquad (66)$$

where D_1 is its diffusion coefficient in the static barrier and S_1 and S'_1 are its solubilities in that barrier and in blood respectively. Similarly for gas II

$$\dot{q}_2 = AD_2 S_2 p_2 = \dot{Q} S'_2 (P - p_2) \qquad (67)$$

where D_2, S_2, S'_2 now refer to gas II p_1 and p_2 are the tensions of the two gases (I and II) in the stirred pool shown in fig. 72 to represent the perfused zone and hence they are also the tensions of those gases in the 'overflow' corresponding to *venous* blood.

Rearrangement of these equations with rationalization by substituting $\alpha = A/x\dot{Q}$, $\beta_1 = D_1 S_1 / S'_1 = D_1 \lambda_1$ and $\beta_2 = D_2 S_2 / S'_2 = D_2 \lambda_2$, where λ is the tissue–blood partition coefficient, enables the supersaturation to be derived from (66) and (67) as

$$p_1 + p_2 - P = \alpha P(\beta_1 - \beta_2)/(1 + \alpha\beta_1)(1 + \alpha\beta_2) \qquad (68)$$

Thus there will be supersaturation of *venous* blood ($p_1 + p_2 > P$) if $\beta_1 > \beta_2$. Hence bubbles will grow if

$$D_1 \lambda_1 > D_2 \lambda_2 \qquad (69)$$

Moreover, in a purely aqueous tissue ($\lambda_1 = \lambda_2 = 1$), all that is necessary for the supersaturation of venous blood is

$$D_1 > D_2 \qquad (70)$$

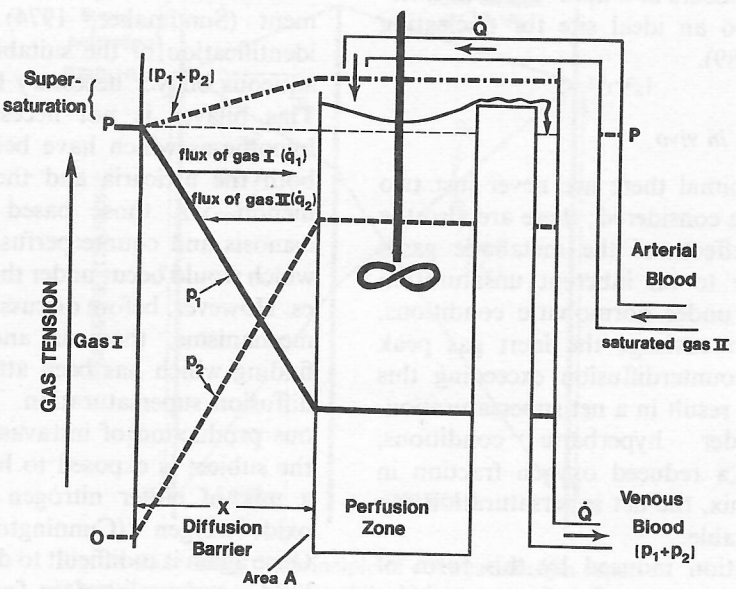

Fig. 72 Illustrating the concept of counterperfusion supersaturation for the case where the more diffusible gas (I) is adjacent to the diffusion barrier at the ambient pressure, while blood is supplied to the perfused zone saturated at the same pressure by the less diffusible gas (II). Note the net supersaturation of the perfused zone by two gases. From Hills (1976a) reproduced by permission of the *Journal of Applied Physiology*

This implies that supersaturation by dissolved gases can occur in any system where a diffusive and a convective resistance lie in series with respect to the counter-transfer of two gases, provided the source of the faster diffusing gas lies adjacent to the diffusion barrier. Numerous transient situations can be envisaged where supersaturation would arise by switching gases (e.g. Harvey and Lambertsen, 1976) but this result is particularly interesting since it applies to *steady-state conditions* so that, if there is nucleation of the convection medium, then bubbles can be produced in it continuously.

Thus counterperfusion supersaturation (Hills, 1976a) would appear to offer a particularly plausible explanation for the *intravascular* bubbles produced continuously in dogs by Cunnington *et al.* (1975). Moreover, it would explain bubble formation within the fluid compartments of the inner ear during nitrogen : oxygen breathing in a heliox environment when any lipid present could be no more than the bimolecular layer of Reissner's membrane. Hence counterperfusion would seem to offer a more likely explanation for isobaric 'vestibular bends' while this mechanism and counter-diffusion supersaturation would seem equally plausible in interpreting isobaric 'skin bends'.

Implications

Counterperfusion supersaturation has implications in gaseous anaesthesia where, if potentiated by elevated pressure, the right combination of gases could produce intravascular bubbles; but these would arise in the venous system where they should be trapped by the lungs.

If sub-symptomatic gas is 'dumped' in extravascular sites during the early phases of decompression from a heliox dive, as would appear likely on many practical tables (p. 164), then these can be regarded as a temporary 'source' of helium. If the diver now switches to air, all of the ingredients needed for counterperfusion supersaturation as depicted in fig. 72 are present. However, the counter-transfer of helium and nitrogen will now supersaturate *blood*, so that an extravascular helium 'dump' will now help to generate an intravascular bubble without rupture of the vessel wall. This is potentially more dangerous and may explain some of the CNS problems developing on transfer from the heliox environment in the diving bell to air in the DDC but, once again, these would be venous bubbles. The corresponding explanation could not be offered by counterdiffusion supersaturation since the lipid needed must be located extravascularly and therefore closer to the helium dump/source than to the aqueous nitrogen source (the blood).

This could also explain the increased incidence of death or serious distress observed in rats exposed to 80 : 20 nitrous oxide : oxygen following decompression on air. Not only would nitrous oxide act as a 'bubble amplifier', as suggested by Van Liew (p. 151), but all of the necessary ingredients are now present for *intravascular* bubbles to be produced by counterperfusion supersaturation, viz. extravascular 'dumps' of nitrogen adjacent to blood freshly equilibrated at the lungs with a slower diffusing gas—nitrous oxide.

The potential for generating *arterial* bubbles by counterperfusion supersaturation could arise in situations where the body is eliminating nitrogen at the lungs while ventilated on heliox. If the airway-to-blood barrier is increased for any pathological reason so that end-capillary blood is not effectively equilibrated with 'alveolar' gas, then appreciable supersaturation could occur in pulmonary venous blood but, in this instance, it would have the much more serious result of producing arterial gas emboli in the systemic circulation, particularly if bubble inception in the lungs is as easy as some studies indicate (Sass, 1976). Hence this argument would suggest caution in switching from air to heliox during decompression, particularly where there could be some lung disease or pulmonary manifestations of oxygen toxicity.

Gas-induced osmosis

The major chemical constituent of the body is water whose displacement between the various tissue compartments can cause numerous disorders, fluid shifts being minimized *in vivo*

by the balance between hydrostatic and osmotic forces. In describing these fine balances, gases are usually ignored or dismissed as having equilibrated across all membranes so rapidly that they exert no influence on homeostasis.

However, for short periods following the start of a rapid change in pressure, there can be quite substantial differentials in gas concentration between blood and tissue, not necessarily across the capillary wall but across more remote diffusion barriers such as the cell membrane. Although these membranes are impermeable to most solutes, they become 'leaky' to smaller molecules. This is often envisaged in terms of 'pores' through which larger solute molecules cannot pass. Thus, as the molecular weight of the solute is reduced, so the osmotic pressure (OP) exerted by the solute is reduced from the maximum value estimated by the van't Hoff expression for a perfectly semi-permeable membrane quoted in classical physical chemistry. In fact, it is reduced by a factor termed the reflection coefficient (σ) which is conventionally explained as the fraction of molecules reflected upon striking the membrane. Thus the osmotic pressure (OP) for a gas with a tension differential across the membrane of Δp is given (Hills, 1972c) by

$$\mathrm{OP} = \sigma S(\Delta p)T/273 \qquad (71)$$

where T is the absolute temperature in degrees Celsius and the solubility (S) is expressed by the Bunsen coefficient to give the OP in the same units as (Δp).

The real question with gas-induced osmosis concerns whether all tissue membranes are so leaky to gases that σ and hence the OP is negligible. Using a synthetic membrane specifically formulated to be impermeable to a very soluble gas (nitrous oxide), Kylstra *et al.* (1968) detected a slight transient shift of water

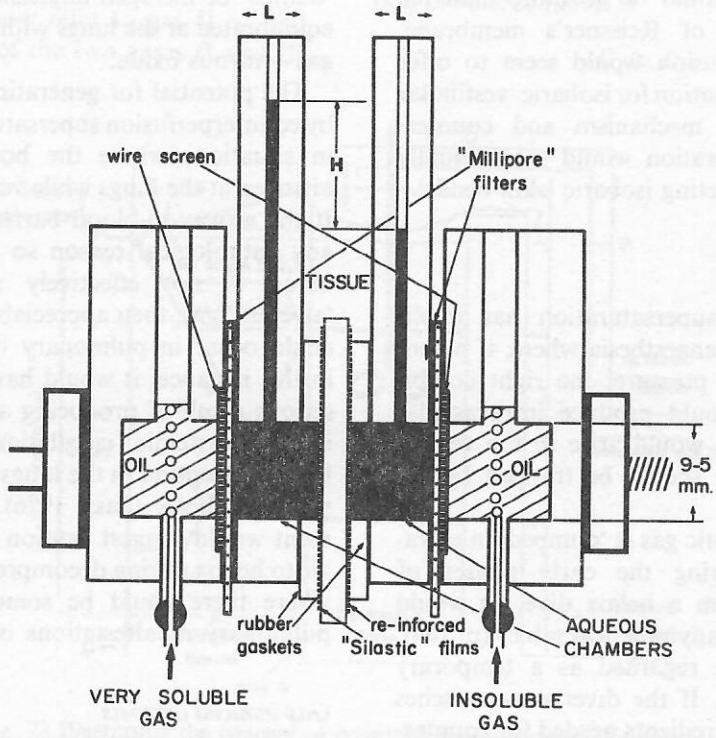

Fig. 73 A differential osmometer in which a steady-state gas concentration gradient is maintained across a tissue section by bubbling a soluble and a relatively insoluble gas through well stirred oil compartments in contact with opposite ends of the aqueous system. The aqueous fluid is physiological saline whose final difference in levels (H) is the net osmotic pressure

towards the nitrous oxide solution when the two were used in a conventional osmometer. In order to test it on *biological* material, Hills (1971b) preferred to use a steady-state method (fig. 73). This maintains gradients of two different gases (e.g. nitrous oxide and nitrogen) in opposite directions in the same manner as in counterdiffusion so that, unlike classical physico-chemical measurements of the OP, gas molecules are replaced as soon as they leak across the membrane. This has produced significant osmotic pressures corresponding to a reflection coefficient of $\sigma = 0{\cdot}05$. This is small compared with $\sigma = 1$ for a perfectly semi-permeable membrane but can still give an appreciable OP for a large gradient ($\Delta p\uparrow$) of a very soluble gas ($S\uparrow$) (see Equation 71). In fact, the σ value for nitrous oxide is just about what would be predicted by extrapolation of values for non-gaseous substances indicating that, in solution, gases are really no different to any other solute after allowing for molecular weight and structure (fig. 74).

Differential analysis by dye dilution of fluid in subcutaneous pockets of different gases in the same animal has provided direct evidence for gas-induced osmosis *in vivo* (Hills, 1971b); while Longmuir and Grace (1969) have shown transient volume changes in red cells very rapidly exposed to nitrous oxide solutions *in vitro*.

Gas-induced osmosis has two major categories of implication:

(1) the transient gradients of inert gases which can exist after rapid compression or decompression where fluid shifts reach a peak (fig. 75) but after the gas has equilibrated across the membrane the fluid assumes its original distribution under the normal homeostatic forces; and

(2) permanent gradients arising from the metabolic gases, particularly when these

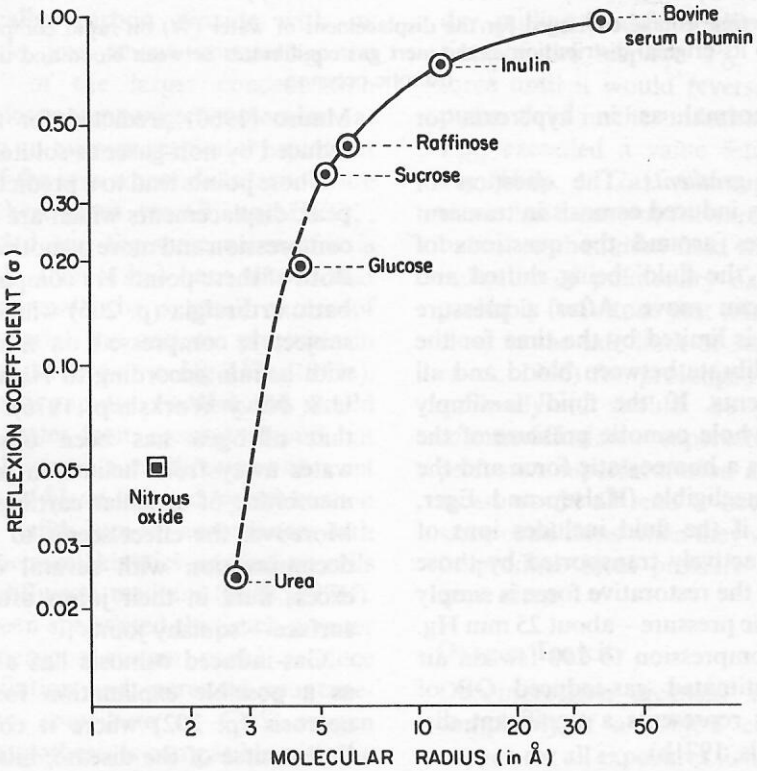

Fig. 74 Reflection coefficients (σ) for several non-volatile solutes across bladder (Davson, 1964) plotted against molecular radius, together with a value for nitrous oxide. From Hills (1972a)

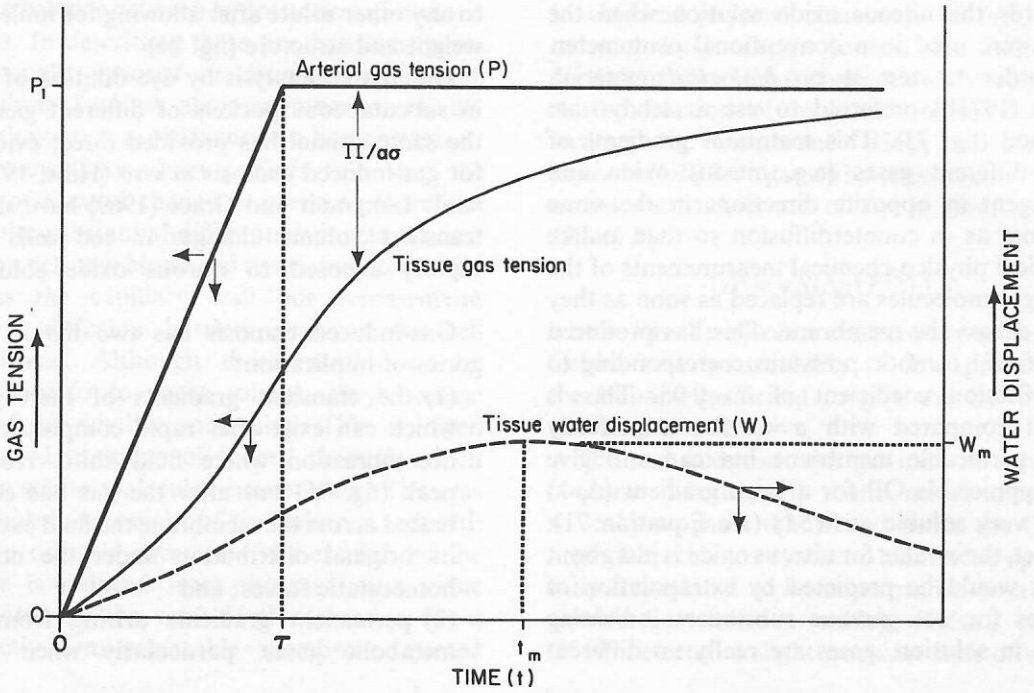

Fig. 75 The time course envisaged for the displacement of water (W) on rapid compression, water returning to its original distribution as the inert gas equilibrates between blood and tissue. Π is the osmotic pressure

differ from normal as in hyperoxia or hypocapnia.

Transient gas gradients The question of significance of gas-induced osmosis in transient situations revolves around the questions of what constitutes 'the fluid' being shifted and how rapidly it can move. After a pressure change, the shift is limited by the time for the inert gas to equilibrate between blood and all tissue compartments. If 'the fluid' is simply water, then the whole osmotic pressure of the fluid would act as a homeostatic force and the shift would be negligible (Halsey and Eger, 1973). However, if the fluid includes ions of which many are actively transported by those membranes, then the restorative force is simply the colloid osmotic pressure—about 25 mm Hg. Hence a rapid compression to 200 fsw on air producing an estimated gas-induced OP of 3·1 mm Hg now represents a significant displacing force (Hills, 1971b).

Moreover, measurements of the rate of osmosis (Hills, 1972a) indicate that fluid shifts occur by hydrodynamic flow rather than by diffusion i.e. 800–900 times faster, just as Mauro (1960) predicted for flow osmotically induced by non-gaseous solutes.

These points lead to a prediction of significant peak displacements which are higher for faster compression and more osmotically potent gases. Both of these points are compatible with hyperbaric arthralgia (p. 206) which is worse if the subject is compressed on nitrogen compared with helium according to Harvey (comment at U.S. Navy Workshop, 1976). It is interesting that nitrogen has been observed to 'pull' water away from helium in solution across a membrane of articular cartilage (Hills, 1971e). Moreover the effect seems to be reversible on decompression with several divers reporting excess fluid in their joints after return to the surface—'squishy joints'.

Gas-induced osmosis has also been offered as a possible explanation for aseptic osteonecrosis (p. 202) where it could explain the time course of the disease, bilateral symmetry, and the occurrence of the disease in submarine escape (James, 1945) and escape training (Elliott, 1974) where there is very rapid compression. This raises the possibility of compression

tables for normal diving. Gas-induced osmosis has already been used as the basis for formulating compression to very great depths with the implication that it is involved in the HPNS (Chouteau *et al.*, 1971), while it might be responsible for the transient component of inert gas narcosis (Hills, 1971b). This is based on the simple reasoning that rapid compression will tend to dehydrate the various parts of the nervous system and so reduce spontaneous activity, a 10% water reduction in the pedal ganglion of the snail reducing the number of spikes from 16–20 to 2–4 per min (Hughes and Kerkut, 1965). However, subsequent electrophysiological measurements in the large neurones of the *aplysia* have indicated that any effect is likely to be small (Blankenship *et al.*, 1976).

Steady-state gradients

The permanent gradients of the metabolic gases, oxygen and carbon dioxide, will oppose each other osmotically, carbon dioxide with its larger molecule just about countering the osmotic 'pull' of the larger concentration gradient of the less potent oxygen molecules—at least, assuming an average respiratory quotient of about 0·8. If the ions whose distributions are influenced by these gases, viz. Cl^- and HCO_3^-, are also included and the same value of σ is assumed for all, then it has been shown that there would normally be a small excess of venous over arterial gas osmotic pressures in peripheral tissues of $3{\cdot}44\sigma$ mm Hg (Hills, 1972a).

If the oxygen is rapidly elevated, this would initially move water from tissue to blood but would eventually reach a steady state with a net water shift *out of blood* induced by the carbon dioxide as it builds up in accordance with standard biochemical kinetics applied to cells as a uniform diffusion medium (Hills, 1971f). Hence it has been speculated that such a water shift in the nervous system could produce intracellular dilution and increased spontaneous activity to contribute to CNS oxygen toxicity. This hypothesis is compatible with the superimposed effects of transient gradients of inert gases (and oxygen) in promoting or suppressing convulsions (Hills, 1972b). Thus, further rapid *compression* on pure oxygen has been found to produce an *abatement* of seizures lasting for several minutes!

If blood carbon dioxide is rapidly decreased by voluntary hyperventilation, there is a marked decrease in blood volume (Straub and Bühlmann, 1970), compatible with extravascular carbon dioxide pulling water away from plasma osmotically.

In the lung, it has been shown that individual ventilation of the two lungs of a rabbit, one with air and the other with 80:20 nitrous oxide: oxygen results in a relative hydration of the nitrous oxide lung under steady-state conditions (Hills, 1972c). This has been explained by suggesting that one lung acts as a source for the more potent osmotic gas and a sink for the other and vice versa for the other lung. If, as this experiment indicates, the pulmonary membrane is partially selective to different gases, then it is interesting to speculate whether the permanent A–V gas osmotic difference mentioned earlier helps to keep the airways dry, pulling fluid from alveoli to blood. Elevation of the inspired P_{O_2} would reduce this force until it would reverse and then tend to pump fluid in the undesirable direction if the P_{IO_2} exceeded a value estimated as 293 mm Hg (Hills, 1972a). Although gas-induced osmosis has been put forward as a factor contributing to the initial fluid shift seen as the first indicator of pulmonary oxygen toxicity, it is probably fortuitous that this value should lie so close to the safe limit of 300 mm Hg (Spencer *et al.*, 1966) for prolonged oxygen breathing.

Finally it should be pointed out that counterdiffusion supersaturation, counterperfusion supersaturation and gas-induced osmosis would all tend to occur under much the same conditions when they would all be tending to produce local pressure differentials in the same sites.

Oxygen Toxicity

Decompression sickness would be avoided completely if a subject could breathe pure oxygen for all exposures. Unfortunately, despite the fact that life is totally dependent upon an adequate supply of this gas, oxygen proves toxic in excessive amounts and has some most unpleasant ways of showing that toxicity.

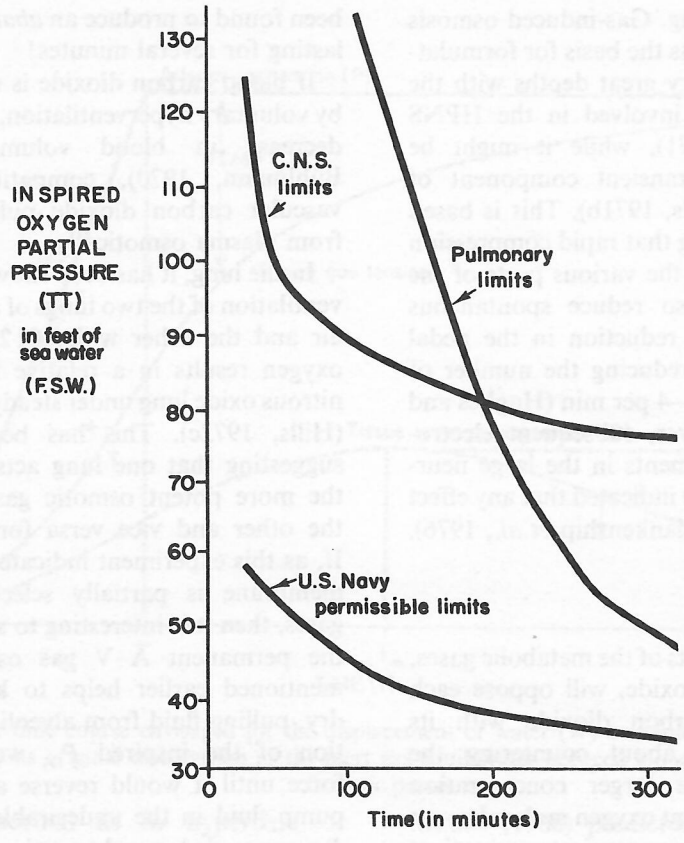

Fig. 76 Pulmonary and CNS tolerance to oxygen in men at rest (Lambertsen, 1967) together with the safe limits for working divers advocated by the U.S. Navy (1974)

Table 16 Oxygen partial pressure limits

	Normal		Exceptional	
Time (t) (min)	Inspired P_{O_2} (ATA)	Increase (Π) (fsw)	Inspired P_{O_2} (ATA)	Increase (Π) (fsw)
30	1·6	46·2	2·0	59·4
40	1·5	42·9	1·9	56·1
50	1·4	39·6	—	—
60	1·3	36·3	1·8	52·8
80	1·2	33·0	1·7	49·5
100	—	—	1·6	46·2
120	1·1	29·7	1·5	42·9
180	—	—	1·4	39·6
240	1·0	26·4	1·3	36·3
	$P_{IO_2}^{\uparrow}$	$(P_{IO_2}^{\uparrow} - 0{\cdot}2)33$		

Data taken from U.S. Navy Diving Manual (1974a).

These symptoms become apparent if the oxygen exposure exceeds certain limits which are most conveniently described by a dose–time curve relating inspired P_{O_2} to time. These marginally safe limits (fig. 76) resemble the bounce-dive curves for decompression sickness but are not so easy to define due to the greater variability between individuals and between successive exposures of the same individual.

Importance of optimizing the oxygen exposure

It is tempting to avoid the problem of oxygen toxicity simply by keeping to oxygen levels far below the toxic limits but one is then losing much of the advantage which a higher partial pressure can provide in both accelerating decompression and expediting treatment. It has long been appreciated by proponents of the more conventional supersaturation theories, and by Haldane himself (Haldane and Priestley, 1935), that the substitution of oxygen for inert gas in the breathing mix is beneficial, since the additional P_{O_2} in the alveoli is not reflected at the tissue level while the corresponding reduction of inert gas *is* (p. 24). However, if critical supersaturation is not the relevant criterion and the other extreme is considered i.e. phase equilibration, then the benefits of higher oxygen become far greater. This can be appreciated from Equation 52 where the driving force for inert gas elimination (ΔP_{N_2}) is almost entirely provided by the inspired oxygen partial pressure, $P(1 - F_{IN_2})$ (see also figs. 40 and 80). Hence it becomes highly desirable to maximize the oxygen exposure but to do this safely it is first necessary to acquire an understanding of the principal features of oxygen toxicity.

Symptomatology

Oxygen toxicity can become manifest in two basically different forms:

(1) neurologic symptoms, reflecting poisoning of the central nervous system. These occur first for high inspired oxygen partial pressures—above about 1·5–2·0 ATS;

(2) pulmonary effects, indicating a slow insidious progression of lung damage. These tend to take over as the presenting symptoms for long exposures to elevated oxygen levels—in excess of 12–15 hours.

If not reversed by return to a normoxic, or at least a sub-toxic environment, continued exposure to a toxic partial pressure of oxygen will produce cellular damage and death in one organ system after another until the process is stopped by pulmonary damage or death (Clark and Lambertsen, 1971).

Neurologic symptoms The onset of neurologic oxygen toxicity can be quite sudden and dramatic, the diver convulsing in a manner virtually indistinguishable from a 'grand mal' epileptic seizure. This is particularly dangerous with a non-tethered diver because the man 'blacks out' and is then totally dependent upon others for his rescue. This poses another problem, since the tongue-chewing, choking nature of the convulsion can easily lead to 'burst lung' and hence to arterial air embolism if he is decompressed in that state. Hence the practice of breathing pure oxygen or oxygen-enriched mixes in the water is not to be recommended. Moreover, in certain closed-circuit SCUBA sets, a careful check needs to be kept to prevent malfunction of the control mechanism sensing the P_{O_2} and then supplying pure oxygen, as needed, to 'make-up' the oxygen in the recirculating gas.

Normally divers do not breathe mixtures high in oxygen during decompression until they are in a chamber with another diver and it is supplied to them by mask from the built-in breathing system (BIBS). In the event that one does convulse, the other diver takes off his mask, if the thrashing of his arms has not already done so and he returns to normal within a few minutes of breathing chamber gas. This must be kept at a P_{O_2} well below toxic levels to reverse the symptoms rapidly. Failure to return him to a sub-toxic environment may result in permanent paralysis or death.

Other manifestations of neurologic oxygen toxicity include dizziness, nausea, tunnel vision, retinal damage, blindness, unusual fatigue, anxiety, confusion and a lack of coordination in movements. Muscular twitching—particularly lip-twitching—can precede a convulsion but no reliance can be placed on this as an early warning. Numb or tingling fingers and

toes have also been implicated as early signs of neurologic oxygen toxicity.

Pulmonary oxygen toxicity This is more common in 'saturation' diving where the diver has had a long exposure to an oxygen partial pressure which may have been substantially above normal. It is sometimes referred to as the 'Lorraine Smith effect' after its delineation by Smith (1899) who showed a progressive hydration of the lungs under hyperoxic conditions leading to greater mechanical difficulties in ventilation together with impaired gas transfer. Thus the diver finds it harder to breathe; he may then feel a deep substernal pain and if not returned to a sub-toxic breathing mix he may gradually become hypoxic as the alveolar walls swell and the oedema increases the air–blood barrier to oxygen diffusion. Thus the paradoxical situation can be reached in which elevation of the oxygen level in the gas ventilating the lungs is actually decreasing blood oxygenation in the pulmonary capillaries.

This can progress to a point of no return where the hypoxia would result in death unless the alveolar P_{O_2} were elevated to increase the oxygen diffusion gradient needed to elevate arterial P_{O_2}. This *does* provide temporary relief but causes further oedema and a slow return of the hypoxia until a still higher inspired P_{O_2} is then needed and so the subject enters a vicious cycle which can only terminate in death. This has not occurred in diving but has done so in intensive care units for respiratory patients for some of whom an inspired P_{O_2} as low as 300 mm Hg can be toxic (Spencer *et al.*, 1966), while Lambertsen (1965) has put the limit at around 350 mm Hg. Another example of the insidious nature of pulmonary oxygen toxicity is the diver who, even twenty-four hours after completing an asymptomatic 'saturation' dive, complains of undue breathlessness when running for a bus.

Despite the gradual onset, there is no reliable indicator; although many parameters of pulmonary function have been studied for this purpose, particularly the vital capacity (Clark and Lambertsen, 1971).

Other symptoms of oxygen toxicity in general include acidosis, testicular damage and erythrocyte haemolysis. However, in the more advanced phases of pulmonary damage, the effects are essentially those of hypoxia.

Hypoxia

When arterial P_{O_2} falls below 70–80 mm Hg, the subject feels drowsy and has difficulty in thinking clearly, often displaying euphoria and other behaviour resembling alcoholic intoxication. Hence the early onset is sometimes mistaken for nitrogen narcosis. At lower oxygen levels, i.e. P_{aO_2} around 60 mm Hg, there is distinct discomfort and hyperventilation until, below 50 mm Hg, some will become comatose with or without passing through hypoxic seizures. Below an arterial P_{O_2} of 30 mm Hg, anyone will pass unconscious and death will ensue at lower oxygen levels. Although some of these symptoms may resemble neurologic oxygen toxicity, hypoxia is characterized by cyanosis clearly visible at the lips and fingernails.

Features of oxygen toxicity

The factors influencing clinical oxygen toxicity have been covered in detail by Bean (1965). Individual variation in susceptibility is much more pronounced in oxygen toxicity than in decompression sickness, in fact to the extent that the U.S. Navy (1974) recommend an oxygen tolerance test (30 min at an inspired P_{O_2} of 120 fsw) to detect subjects who are hypersensitive to oxygen.

Oxygen toxicity can be potentiated by elevated carbon dioxide and by virtually every factor which increases metabolic rate. This is particularly true of exercise which can reduce the onset time of neurologic symptoms from 3 hours to 10 min at an inspired P_{O_2} of 3 ATS for just a three-fold increase in metabolic oxygen consumption (Behnke *et al.*, 1935a). Comparable ratios appear to hold for pulmonary symptoms. Hence it is much safer to administer elevated oxygen during decompression when the divers are resting in a deck decompression chamber. There are a multitude of other factors which affect metabolic rate and hence the imminence of oxygen toxicity

but among the more obvious are food intake, diet, temperature and time of day. Inert gases can influence the imminence of oxygen toxicity but the data is somewhat conflicting (Clark and Lambertsen, 1971) and may also reflect the marked effect of *switching* mixes rather than the nature of the inert gas itself (p. 217).

There is also the interesting feature that a man will often convulse during the decompression following a marginally safe exposure to hyperbaric oxygen (Hill, 1912). Oxygen must be regarded as having a dual role in its very complex effect on the central nervous system where, in such transient situations, it can demonstrate its narcotic action, possessing a potency estimated as 2·8 times that of nitrogen (Paton, 1967). However, narcosis becomes manifest much sooner than oxygen toxicity. Thus decompression is removing the depressant effect of oxygen as a narcotic (plus any inert gas present) on the central nervous system at a time when oxygen, as a metabolic gas, has had time to build up its toxic insult. Hence decompression *per se* will predispose the subject to a convulsion. The same applies to a lesser extent on taking off the mask through which a subject has been breathing an oxygen-enriched mixture. The switch to chamber mix, although at the same pressure, results in a sudden substitution of a less narcotic gas for much of the oxygen previously inspired on BIBS. This tendency to convulse on returning to chamber mix has been termed the 'mask-off' effect.

A number of drugs have been tried in various attempts to prevent oxygen toxicity but those proposed so far either afford only partial protection or unduly impair the diver's ability to work.

Mechanisms

Although it is unnecessary to know the mechanism of oxygen toxicity to prescribe oxygen, the wide range of hypotheses which have been proposed gives some indication of the complexity of the problem and hence the difficulty in finding a pharmacological solution.

The neurotoxic actions of high pressure oxygen are generally accepted to be ultimately due to a direct biochemical effect (Haugaard, 1968), many mechanisms implicating the oxidation of enzymes—either those associated with the permeability of membranes or those essential to some vital metabolic pathway. The final list includes:

(1) The inability of blood to remove carbon dioxide from tissue when haemoglobin is still saturated with oxygen—even in the venous system (Gesell, 1923). This hypothesis can easily explain potentiation by carbon dioxide and is based on known competition between oxygen and carbon dioxide for the sites on Hb molecules as demonstrated by the Bohr and Haldane effects (p. 24).

(2) The oxidation of various 'membrane associated' enzymes leading to a change in structural integrity and hence permeability (Wolman, 1963). This can easily provide the essentially *local* nature of the primary insult needed to explain the evidence on pulmonary oxygen toxicity (Clark and Lambertsen, 1971).

(3) Inhibition of enzymes and coenzymes by lipid peroxides known to be formed in animal brains during exposure to hyperbaric oxygen (Zirkle *et al.*, 1965). This is compatible with the rapidly reversible nature of neurologic oxygen poisoning (Lambertsen, 1955).

(4) Increase in the concentration of free radicals which can then attack vital tissue constituents to disrupt cell function (Gerschman, 1964). Moreover toxicity could become manifest when the production of superoxide radicals exceeds the known capability of superoxide dismutase to catalyse their deactivation (Fridovich, 1972).

(5) Numerous theories based on changes in oxidative metabolism recently reviewed by Wood (1975).

(6) A direct toxic action of oxygen on the smooth-muscle fibres which are the mechanical elements in arteriole walls implementing the known cerebral vasoconstriction induced by high-pressure oxygen (McDowall, 1966;

Saltzman *et al.*, 1964; Ledingham *et al.*, 1966). This approach is compatible with oxygen convulsions being precipitated by the breakdown of this vasoconstriction (Bean *et al.*, 1972).

(7) The oxygen-induced vasoconstriction can cause a gradual depletion of nutrients in the arteriole walls until the muscle fibres are forced to relax (Bean and Leatherman, 1969). This would lead to a cyclic mode of vascular breakdown as vessel tone was periodically restored, not unlike the intermittent nature of seizures as they are observed at the onset in some animals.

(8) Elevated blood oxygen causes a redistribution of cellular carbon dioxide and oxygen according to standard biochemical kinetics applied to cytoplasm as a uniform diffusion medium, resulting in an osmotic gradient tending to hydrate the cell (Hills, 1971f). This is compatible with the tendency for giant neurones to fire in response to reduced osmalality (Hughes and Kerkut, 1965) and can explain the effects of switching inert gases and rapidly changing inspired P_{O_2} where rapid compression on pure oxygen can give temporary remission from seizures. Gas-induced osmosis also has direct pulmonary implications (p. 217).

(9) Another 'physical' mechanism attributes the convulsion to the gradual elevation of brain temperature due to the lack of replacement of oxygen with carbon dioxide on the haemoglobin molecule within the capillary bed and hence the absence of any chemical absorption of metabolic heat by blood (Hills, 1973b). Hyperthermic subjects are known to be most susceptible to neurologic oxygen toxicity (Fenn, 1969).

This list may represent some overlap between physiological mechanisms and their underlying biochemical causes. In addition to this wide variety of biochemical, physiological and physical approaches, it is well known that hyperbaric oxygen affects the endocrine system (Bean, 1951). The final answer will probably be a combination of a number of these factors but the need to optimize oxygen exposure cannot wait until these are elucidated.

Oxygen limits

Despite the multiplicity and complexity of the mechanisms proposed, the limits for safe oxygen exposure are reasonably well defined. These are shown separately for neurologic and pulmonary symptoms in fig. 76. The same data

Table 17 Mean survival time of different species in continuous 100% O_2*

Source	Species	Pressure (atm)	Mean survival time ± S.D.
Hiatt	mice	1·0	120 hr
Hiatt	mice	1·0	144 hr
Wright	mice	1·0	141 hr ± 50·4
Ackermann	rats	3·0	9 hr
Ackermann	rats	2·0	15 hr
Barach	rats	1·0	8·3 hr
Penrod	guinea pigs	5·5	1·9 hr ± 0·5
Penrod	guinea pigs	4·0	2·9 hr ± 1·2
Hall	guinea pigs	3·0	12·4 hr ± 2·7
Lambertsen	guinea pigs	3·0	8·6 hr ± 3·5
Ackermann	rabbits	2·0	17 hr
Barach	dogs	1·0	56·7 hr ± 37·4
Paine	dogs	1·0	39 hr
Dolezal	man	1·0	153 hr ± 36·6
Caldwell	man	1·0	106 hr ± 37·4

*Data taken from Lambertsen (1970).

are given in tabular form for the first six hours in Table 16, together with the differences (Π) above a normal inspired P_{O_2} of 0·2 ATA.

There is a controversy concerning the P_{IO_2} to be used for very long periods under pressure, survival times for various species being given in Table 17. However, for man, the original figure of 428 mm Hg given by Behnke *et al.* (1935a) as the irritant level for prolonged oxygen breathing provides a conservative figure of 0·5 ATS as a safe limit.

However, in most practical diving, we are not dealing with a fixed partial pressure of oxygen but with one which can often vary quite widely as the diver moves between decompression stops and switches breathing mixes. Two calculation methods have been proposed to allow for such irregularity in the oxygen history in attempting to quantify the imminence of toxic manifestations at any stage of the dive. These two basically different approaches employ the following cumulative parameters: units of pulmonary toxicity dose (UPTDs); and a cumulative oxygen toxicity index (COTi).

Unit pulmonary toxicity dose

This approach has been developed by Lambertsen (1970) based on the theses of Feld and Clark at the University of Pennsylvania. It is aimed at predicting the degree of pulmonary distress from the number of units accumulated during the dive up to the point in question.

Each unit, or 'unit pulmonary toxicity dose' (UPTD), is defined as the degree of pulmonary toxicity produced by breathing oxygen at a partial pressure of 760 mm Hg (1·0 ATA) for one minute. If the subject breathes this particular partial pressure for two minutes, he has accumulated two units and so on, such that the total of UPTDs is progressively increasing with time. On the other hand, the UPTD is not assumed to be proportional to the oxygen partial pressure (p) but is effectively

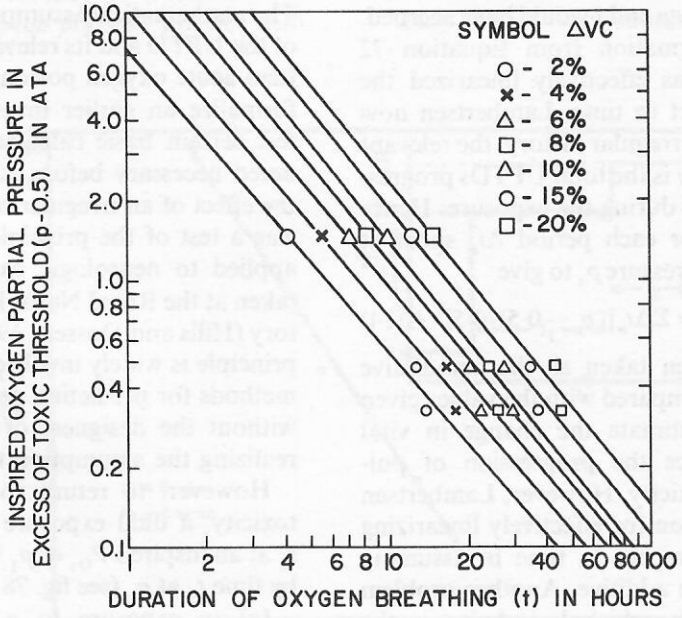

Fig. 77 Inspried P_{O_2} in excess of the toxic threshold of 0.5 ATA plotted against time for equal decrements in vital capacity (VC). Parallel straight lines drawn through points of equal ΔVC form the mathematical basis of the unit pulmonary toxicity dose (UPTD). Redrawn from Lambertsen (1970), quoting the work of Clark

weighted in accordance with the log–log plots shown in fig. 77. This figure depicts experimental points for partial pressure in excess of the assumed 0·5 AT minimum toxic level, i.e. $(p - 0{\cdot}5)$, versus time of exposure (t). Although three scattered points hardly define any relationship, especially on a log–log plot, straight lines have been drawn—one through each set of points. These have then been expressed by the following equation relating a general exposure (p, t) to a standard exposure (p_1, t_1):

$$\log(p - 0{\cdot}5) - \log(p_1 - 0{\cdot}5) = u(\log t - \log t_1) \quad (72)$$

where the 'pulmonary index' (u) is the slope of the lines in fig. 77 from which it has been estimated as $-1{\cdot}2$. Substituting this value for u, Equation 72 can be rearranged to give the equivalent time (t_1) for a standard exposure $(p_1 = 1 \text{ AT})$ as

$$t_1 = t[(p - 0{\cdot}5)/0{\cdot}5]^{1{\cdot}2} \quad (73)$$

Hence, from the definition of the UPTD, t_1 is now the number of units which the simple exposure defined by p and t would have accrued. Since the transformation from Equation 72 to Equation 73 has effectively linearized the UPTD with respect to time, Lambertsen now argues that, for an irregular history, the relevant indicator of toxicity is the total UPTDs progressively accumulated during the exposure. Hence he adds a term for each period Δt_n spent at an oxygen partial pressure p_n to give

$$\text{Total UPTDs} = \Sigma \Delta t_n[(p_n - 0{\cdot}5)/0{\cdot}5]^{1{\cdot}2} \quad (74)$$

This total is then taken as the cumulative dose and can be compared with the values given in Table 18 to estimate the change in vital capacity and hence the progression of pulmonary oxygen toxicity. However, Lambertsen offers no justification for effectively linearizing the UPTD with respect to time in assuming that these units are additive. Another problem with this approach, which he admits, is the fact that the total cannot decrease as the toxicity recedes when the subject is exposed to sub-toxic oxygen levels. His work shows that intermittent return to a sub-toxic breathing mix may delay chronic oxygen toxicity indefinitely (Lambertsen, 1955) and yet total UPTDs cannot decrease. However, any failure to make allowance in the mathematics for reversal of the toxic process is erring on the safe side, while totals of the order of 1800 units seem to provide a good guide to oxygen exposure from evidence collected in the field.

Table 18 A comparison of 'Unit Pulmonary Toxicity Dose' with corresponding change in vital capacity

Total UPTDs	Corresponding change in vital capacity (ΔVC) in 50% of subjects (%)
615	−2
825	−4
1035	−6
1230	−8
1425	−10
1815	−15
2190	−20

Data taken from Lambertsen (1970).

Principle of superposition

The mathematical assumptions in the derivation of the UPTD and its relevance to chronic rather than acute oxygen poisoning, led this writer to formalize an earlier investigation designed to test certain basic calculation principles considered necessary before attempting to quantify the effect of an irregular oxygen exposure. This was a test of the principle of superposition as applied to neurologic oxygen toxicity undertaken at the Royal Naval Physiological Laboratory (Hills and Dossett, 1968). Incidentally, this principle is widely invoked in many calculation methods for predicting decompression sickness without the designers of those methods fully realizing the assumption they are making.

However, to return to the case of oxygen toxicity, a dual exposure consisting of a time t_1 at an inspired P_{O_2} of p_1 immediately followed by time t_2 at p_2 (see fig. 78 inset) is equivalent to

(a) an exposure to p_1 above normal for time $(t_1 + t_2)$, plus

(b) a superposed exposure $(p_2 - p_1)$ for time t_2.

If it is simply argued that the time course of toxicity is unknown, and follows some un-

known function $\phi(t)$, then the cumulative effect (CE) of the two exposures is now given by the principle of superposition as

$$CE = p_1 \cdot \phi(t_1 + t_2) + (p_2 - p_1) \cdot \phi(t_2) \quad (75)$$

If convulsions are precipitated by the same cumulative effect, i.e. CE has a constant value K, say, for onset, then

$$p_2 = \frac{K}{\phi(t_2)} - p_1 \cdot \frac{[\phi(t_1 + t_2) - \phi(t_2)]}{\phi(t_2)} \quad (76)$$

Hence if t_1 and t_2 are kept constant while p_1 and p_2 are varied, then the principle of superposition would predict a linear relationship between p_1 and p_2 with a negative slope, since $\phi(t_1 + t_2)$ and $\phi(t_2)$ must be constant if t_1 and t_2 are held constant irrespective of the nature of the function. Hence the experimental verification of this form (fig. 78) adds strong support for the concept that the principle of superposition holds for oxygen toxicity—at least for neurologic symptoms in rats (Hills and Dossett, 1968). Moreover, it indicates that acute oxygen toxicity is additive with respect to *oxygen partial pressure* but not with respect to time as assumed in the derivation of the UPTD for chronic oxygen poisoning.

Cumulative oxygen toxicity index

This early work has recently been formalized (Hills, 1976b) into a very simple index to express the imminence of oxygen toxicity—the cumulative oxygen toxicity index (COTi). The principle of superposition can now be applied to any oxygen history whose partial pressure versus time profile (p versus t) is divided into a number of rectangular steps. If, at time t_n *from the start*, the inspired P_{O_2} is switched from p_{n-1} to p_n, then this switch is equivalent to an exposure $(p_{n-1} - p_n)$ for time $(t - t_n)$ up to the point in question. Thus its contribution to the cumulative effect at that point (time t) is $(p_{n-1} - p_n) \cdot \phi(t - t_n)$. Hence the overall cumulative effect (CE) of all changes to that point will be the simple algebraic sum, indicating that symptoms can occur if it exceeds the threshold value (K), i.e. if

$$CE = \Sigma(p_{n-1} - p_n) \cdot \phi(t - t_n) > K \quad (77)$$

This sounds very simple until it is realized

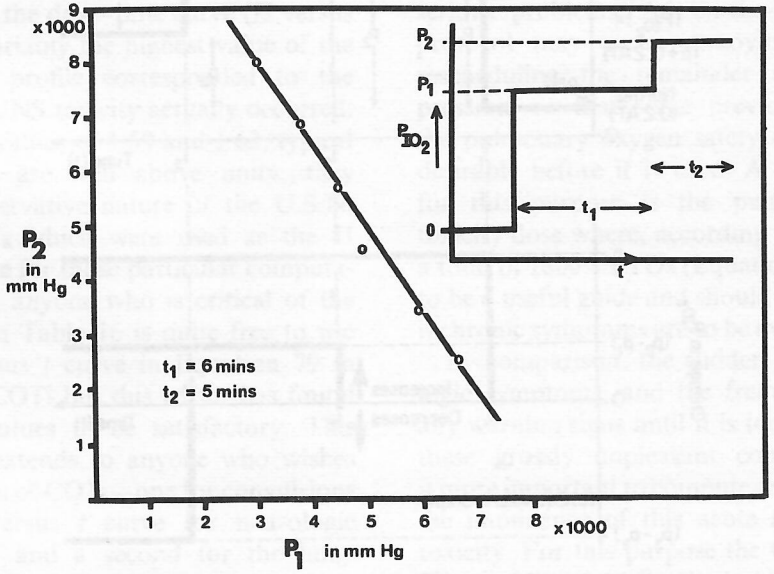

Fig. 78 Combinations of inspired oxygen partial pressures ($P_1 + P_2$) for consecutive exposures (see inset) which produce oxygen convulsions in rats. Redrawn from Hills and Dossett (1968)

that the time function ϕ is unknown. However, the same expression (Equation 77) should hold in the case of either an irregular history or just one constant exposure. If the constant partial pressure of oxygen in excess of normal (0·2 ATS) for symptoms to occur in time $(t - t_n)$ is Π_n, then the marginal condition is expressed by

$$\Pi_n \cdot \phi(t - t_n) = K \qquad (78)$$

The unknown function can now be eliminated from Equations 77 and 78 to define a simple cumulative oxygen toxicity index (COTi) which will indicate that symptoms are likely to occur if

$$\text{COTi} = \Sigma\{(p_{n-1} - p_n)/\Pi_n\} > 1 \qquad (79)$$

For the first step, $p_{n-1} = p_0 = 0{\cdot}2$ ATA; while Π_n versus time is nothing other than the dose–time curve which is readily available for man in fig. 76 and Table 16. Hence the COTi is really reducing each switch in P_{IO_2} to a fraction of the constant P_{IO_2} (Π_n) which would just precipitate symptoms or produce the same degree of distress *in the same time*. These fractions are then added algebraically; that is remembering to subtract from the total those fractions for which p_{n-1} is less than p_n, i.e. where $(p_{n-1} - p_n)$ is negative. Thus this simple index expressed by Equation 79 requires *no mathematics* but just simple arithmetic in which the following steps are followed:

(a) the oxygen history is approximated to a number of rectangular 'steps' in inspired P_{O_2} versus time (see fig. 79);

(b) the time from the start (t) is selected at which the imminence of toxicity is needed to be known;

(c) the time elapsed from each 'step' to that point is then calculated by simple subtraction;

(d) this elapsed time $(t - t_n)$ is then referred to the dose–time curve to give the oxygen partial pressure in excess of normal (i.e. the Π_n value) needed to provoke that type of symptom in that time;

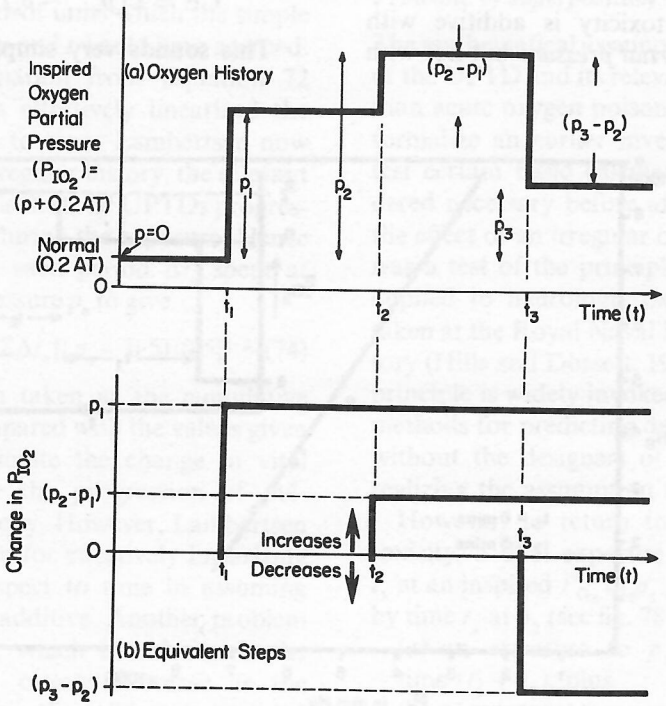

Fig. 79 Illustrating the principle of superposition applied to an oxygen history consisting of four consecutive exposures. Note that decreases in inspired P_{O_2} count as negative steps

(e) this value for constant exposure (Π_n) is then divided into the oxygen switch ($p_{n-1} - p_n$) made at the corresponding *elapsed* time ($t - t_n$);
(f) these fractions (some may exceed unity) are then added algebraically to give the COTi.

Unlike the accumulation of UPTDs where a number is simply added each minute as the dive proceeds, the whole calculation needs to be repeated if the COTi is required at another point on the profile. This arises because t changes every minute and hence, so will all Π_n values.

Validation The COTi has been found to hold to within $\pm 11\%$ for neurologic symptoms in rats exposed to two different oxygen histories each composed of four different yet consecutive oxygen partial pressures (Hills, 1976b), referring each step, of course, to the particular dose–time (Π versus t) curve for convulsions in rats.

Having justified the index on rats, the COTi was then computed at one-minute intervals over various oxygen histories for dives which had actually been performed, including some with high oxygen usage such as published by Bennett and Vann (1975) that had produced convulsions *in man*. These were, of course, computed using the dose–time curve (Π versus t) *for man*. Invariably the highest value of the COTi in each profile corresponded to the point at which CNS toxicity actually occurred. Although peak values of 1·59 and 1·62, typical of convulsions, are well above unity, they reflect the conservative nature of the U.S.N. dose–time limits which were used as the Π versus t reference for those particular computations. However, anyone who is critical of the values quoted in Table 16 is quite free to use his own Π versus t curve in Equation 79 in estimating the COTi but this writer has found these U.S.N. values to be satisfactory. This flexibility also extends to anyone who wishes to use two values of COTi—one for convulsions using the Π versus t curve for neurologic oxygen toxicity and a second for the lung. However, the principle of superposition has not yet been tested for pulmonary manifestations. It is possible that the process leading to their development is not mathematically reversible even though we know that they are physiologically reversible (p. 221). This mathematical reversibility holds for CNS symptoms, since the histories on which the principle of superposition was tested included intermediate steps at sub-toxic levels.

Summary

It is probably fair to say that, with the present state of the art, the mechanism(s) of neurologic and pulmonary oxygen toxicity are not known and we cannot prevent either except by limiting the oxygen exposure. These limits are fairly well defined for *constant* oxygen partial pressures (fig. 76), while the other factors which potentiate the toxic effects of oxygen are clearly recognized.

However, for the practical case of an irregular oxygen exposure, the prediction is more difficult. This writer takes the view that it is always better to use a direct physiological (or pathological) indication of toxicity rather than resort to mathematics. Hence the gradual onset of pulmonary symptoms enable these to be detected early and, hence, enable the oxygen exposure to be changed long before they lead to any serious problems. An on-the-spot change of protocol may prove annoying if it entails rescheduling the remainder of the decompression, so that some previous insight into the pulmonary oxygen safety of a protocol is desirable before it is used. A convenient unit for this purpose is the pulmonary oxygen toxicity dose where, according to Clark (1976), a total of 1800 UPTDs (Equation 74) is proving to be a useful guide and should not be exceeded if chronic symptoms are to be avoided.

By comparison, the sudden onset of neurologic symptoms, and the frequent absence of any warning signs until it is too late to prevent these grossly unpleasant convulsions, make it more important to compute an index depicting the imminence of this acute form of oxygen toxicity. For this purpose the COTi (Equation 79) would seem well suited. Although analyses of published and proprietary tables show convulsions occurring where the index reaches

a value of 1·6, a critical limit of 1·0 is still recommended as a conservative figure allowing for the wide individual variability in neurologic oxygen tolerance. At least, unity is the safe limit based on U.S.N. limits for safe single exposures (Table 16).

Although determination of the COTi requires no mathematical expertise beyond simple arithmetic, much of the tedium can be avoided by using a digital computer (Hills *et al.*, 1976). Moreover, if the imminence of decompression sickness is computed at the same time intervals as the COTi is updated, then the decompression and oxygen toxicity programmes can be interrelated so that not only is depth optimized against time but the oxygen exposure is simultaneously maximized. This can be applied to any model or calculation method for avoiding the bends.

Oxygen computer

While the tedium of calculating UPTDs or a COTi for each one-minute interval in a decompression profile can be alleviated by use of digital computers, this is not particularly practical in many instances. A computer may not be available, nor a programmer when a 'bend' occurs, while the programme itself may need extensive 'debugging' before it will work with the local hardware. Moreover, unless the table designer can write the programme, this may involve divulging proprietary information on decompression acquired at much expense to the diving company. Hence a desk oxygen computer has been produced whereby the designer 'feeds in' his depth–time profile simply by placing pegs in a board in which the matrix of holes are arranged in horizontal rows representing 10 fsw increments in depth and vertical columns representing 1, 2, 5 or 10-min time intervals (Hills, 1976b). He also 'feeds in' the oxygen fraction of each of up to four breathing mixes (see fig. 39). The operator can then select any point at will to obtain an immediate reading of the COTi, without his performing any calculation at all. If a point in the profile appears dangerous, then it can be modified empirically by adjusting depths or mixes or both. The instrument works on the principle of matching the dive history fed in by means of the pegs to the time function represented by a bank of resistors following the U.S.N. dose–time curve, the relative 'mating' of the two being determined by the point on the profile selected for estimating the imminence of oxygen toxicity.

Hence the oxygen computer has two basic uses: to check a decompression profile for oxygen exposure before it is released for use in the field and, secondly, as an on-site unit for providing an immediate estimate of the amount of oxygen treatment which can be prescribed for a diver who has bent without aborting the decompression. Most convulsions occur, in practice, during treatments when the diver has already acquired a complex oxygen history before 'bending' and the medical officer has little way of knowing his proximity to neurologic oxygen toxicity before recommending any therapeutic measures to be followed.

Treatment of Decompression Sickness

Acute decompression sickness should be treated by immediate recompression. Moreover, this should be recommended for any subject seeking medical treatment who has been working in compressed air or otherwise exposed to a hyperbaric environment within the previous day or so. This applies almost irrespective of the presenting symptoms and however well they may appear to follow the pattern of another disease. If modest recompression fails, then the subject can be treated for that other disease but the majority of cases are resolved by this measure or it affords a substantial remission in the symptoms. There are other treatments available such as oxygen breathing, intravenous administration of low-molecular-weight dextran, while various pharmacological approaches have been suggested but, if approved, any of these should be used as an adjunct to recompression rather than as a treatment in itself (Davis *et al.*, 1971).

For comprehensive clinical discussions of the treatment of decompression sickness the reader is referred to the reviews by Griffiths (1969) and Kidd and Elliott (1969).

Recompression

As long ago as 1857 Hoppe-Seyler found recompression to be effective in the treatment of compressed-air illness, long before Paul Bert demonstrated bubbles on recompression or von Schrotter implicated their formation in the aetiology of the disease. The major problems lie in deciding

(a) how far to recompress;
(b) how long to hold that pressure;
(c) how slowly it is then necessary to decompress to prevent recurrence of symptoms; and
(d) what mix to breathe during each stage of this procedure.

These four questions lead to a compromise between the greater effectiveness of an increased recompression exposure and the large amount of additional decompression time which is then incurred in returning the subject to normal pressure. This is particularly acute if the treatment fails or there is some complication difficult to treat in the chamber.

Theoretical considerations

If any symptom develops, then the diver has either not obeyed the prescribed decompression or the method used to formulate it has proved inadequate for that subject on that particular dive. However, once decompression sickness occurs, there is almost universal agreement that the gaseous phase *is* present, so that the major academic controversy surrounding prevention (Chapter 6) is no longer an issue when it comes to treatment. Minimal recompression often gives total relief of limb bends (p. 58) and, moreover, usually does so instantaneously. This writer has observed Okinawan pearl divers and Greek sponge divers who will get relief from a mild bend by sitting immersed up to the neck in a drum of water. This and the immediate reversibility of the effect of ambient pressure leaves little doubt that the pain-provoking process involves the volume of bubbles or gas separated from solution in other shapes. Alleviation of pain is too rapid to represent reversal of blood disorders or to allow time for gas to dissolve. The most rapid reversal of any blood-related disorder induced by recompression which this writer has seen is that of Wells (1975) who demonstrates how the microcirculation can be largely restored within 10–20 minutes of extensive recompression—at least, in the mesentery.

Blood disorders and blood-borne emboli could account for the few cases which do not respond immediately to recompression, Kidd and Elliott (1975) quoting 205 cases of Type I decompression sickness in which only four (2%) failed to get relief. On the other hand the failure rate was 13% for Type II symptoms, largely confirming a different mechanism (Chapter 3) in which recompression is less likely to remove an occlusion than it is to reduce the distortion of a nerve ending by a bubble.

While a limb bend will eventually disappear in a few hours if the pain can be tolerated, this is often not true of CNS symptoms. Moreover, delay in administering treatment to these Type II 'hits' reduces the chances of success, the probability of residual symptoms rising from 1% in cases treated within 30 min to 13% if treated within 6 hours of onset according to one estimate (Rivera, 1964). However, there are cases where successful recompressions have not started until 4–7 days post-dive, so it is always worth trying. This is compatible with the concept that whereas bubbles can be resolved by recompression, this would not apply to the incompressible products of blood degradation which intravascular gas could cause if left untreated for some time. However, the number of Type II cases which *can* be treated successfully by recompression indicates that the entities causing occlusion are compressible and hence gaseous. These gas emboli, however, are likely to need to be removed to restore blood flow to that part of the CNS, whereas an extravascular bubble pressing on a nerve ending only needs to be reduced to a sub-threshold size to alleviate limb bends (see fig. 18). This line of reasoning is compatible with the observation that greater recompression, i.e. an average recompression ratio of 1·9 is needed to relieve Type II decompression sickness compared with

1·5 for Type I according to data from Kidd and Elliott (1975).

Thus the rationale underlying treatment reduces to

(1) recompress to reduce the volume of separated gas, either to decrease the pressure of a bubble on a nerve ending to a sub-critical level for provoking pain or displacing it from the vessel it is occluding; and then

(2) dissolving the compressed gas so that it does not expand to its previous volume on subsequent decompression.

The second involves time and need not apply if the first step has already removed it from a critical location, when the optimal pressure for the slow process of dissolving the bubble need not coincide with the pressure for relieving pain or dislodging the embolism.

Level of Recompression

There are three schools of thought on this:

(a) recompress to the level of relief;

(b) recompress to the previous working depth; or

(c) recompress to the pressure corresponding to the first stage of a standard treatment schedule.

Theoretically, the greatest pressure should provide both the greatest reduction in bubble size and the largest driving force for bubble resorption. This is expressed quantitatively in the expression for the gas phase present (Equation 52) where increasing pressure (P) on a given breathing mix (F constant) increases the driving force (ΔP_{N_2}) for inert gas elimination from the tissue. Moreover, this expression applies after a steady state has been attained on recompression, i.e. *after* the increased capacity of the tissue for dissolved gas at the higher pressure has been taken up by both gas from the bubble and gas from blood. Although the driving force (ΔP_{N_2}) can be greatly increased by compressing well beyond the point of relief of pain in limb bends it has been shown that the rate of nitrogen elimination from large pockets of gas does not increase proportionately (Van Liew, 1971). Recompression to the point of pain relief has the advantage of minimizing the likelihood of compressing any sub-symptomatic intravascular bubbles filtered out of the venous system by the lung to the stage where they can pass through to the arterial system and cause the much more serious symptoms of Type II decompression sickness. In this connection, it is perhaps pertinent to recall the verbal accounts one hears of divers emerging from decompression with no symptoms, neither Type I nor Type II, who have accompanied a colleague to pressure who has a limb bend only to develop a CNS 'hit' themselves.

CNS symptoms

While there is a good case for minimal recompression in the treatment of Type I decompression sickness, this is not necessarily the best advice for Type II 'hits' which are much more serious in that they are more likely to lead to permanent paralysis or death. Thus every action is taken to effect a cure irrespective of the time involved.

Recompression must be started immediately to ensure a successful treatment, so it is fortunate that most Type II symptoms arise soon after decompression when the diver or caisson worker is still in the vicinity of the pressure chamber. It is generally understood that this removes the occlusion before the ischaemia can cause permanent damage. Animal studies have shown that treatment at the standard U.S.N. recompression pressure for these symptoms of 6 ATA (165 fsw) removes most bubbles visible in a cranial window (Waite *et al.*, 1967). However, subsequent use of this preparation in guinea pigs and measurement of total gas in excised whole brain has shown that 80–90% of total brain gas is removed simply by the recompression which deposits gas into the venous system (Grulke, 1975; Hills and Grulke, 1975). Moreover, later work showed that a bounce compression to 200–300 fsw and back was even more effective. This deep 'bounce' of no more than one minute offers the mechanical advantage of clearing the obstructions

posed by the bubbles without the disadvantage of tissues taking up any significant amount of gas to be eliminated later. This would suggest a short deep bounce as a pre-treatment for a Type II 'hit', returning to the pressure at which the normal treatment table would be started with the intention of dissolving any gas which the pre-treatment had not dislodged. Although there are unconfirmed reports of deep bounce pre-treatments having been used successfully on men in the field, it did coincide with some unexplained deaths in guinea pigs, so the suggestion must be regarded as experimental. It would certainly not be recommended for *limb bends*, since it could cause the lungs to release trapped bubbles into the arterial system (Hills and Grulke, 1975). Moreover, there is little point in temporarily reducing the size of bubbles probably trapped in extravascular locations in Type I (p. 58) where they would simply expand to their original size in the same pain-provoking sites on return to their original pressure. Blankenhorn *et al.* (1942) has demonstrated how limb bends recur *in the same sites* following deep recompression.

Recompression time

This need to take the time to dissolve such gas deposits causing limb bends is reflected in the U.S.N. treatment tables (Table 19). With oxygen available, Type I decompression sickness can be treated by 45 min at 60 fsw plus 90 min decompression (Table 19, V) if pain is relieved within 10 min or, if not, the period at 60 fsw is extended to 75 min for an overall 285 min (Table 19, VI). When oxygen is not available, cases relieved by 66 fsw are treated at 100 fsw for 30 min followed by 350 min of decompression (Table 19, IA), while more extensive compression is recommended for more persistent limb bends by going to 165 fsw for 30 min for a total exposure of 659 min (Table 19, IIA). For more serious symptoms the recommended re-recompression pressure is always 6 ATA (165 fsw) on air for 30 min if oxygen cannot be used and symptoms are relieved within that time (Table 19, III) or up to 90 min if not (Table 19, IV) to give a total recompression time of 2260 min. If oxygen is available, this can be reduced to 154 min if symptoms are relieved within 15 min (Table 19, VA) or 319 min (Table 19, VIA) if they 'moderate to a major extent' within 30 min.

Use of oxygen

This substantial reduction in total treatment time with oxygen breathing can once again be appreciated from the form of Equation 52 where a switch to pure oxygen ($F_{IN_2} = 0$) greatly increases the driving force (ΔP_{N_2}) for nitrogen elimination *from separated gas*. The great benefits to be derived from oxygen breathing during treatment were clearly demonstrated by Goodman and Workman (1965) on whose work the present U.S.N. therapeutic schedules are largely based.

However, it should be remembered that these benefits are not just derived from substituting oxygen for nitrogen in blood but by doing so at the highest pressure (P) which avoids oxygen toxicity, when the increase in the driving force for bubble resolution (ΔP_{N_2} in Equation 52) undergoes a disproportionately greater increase (see fig. 80). Oxygen is interspersed with periods of air breathing to avoid oxygen toxicity for the reasons outlined in the previous section.

These recommendations and others have now been put into the form of a superb chart of recompression treatment instructions which is particularly easy to follow and has been included in the latest U.S. Navy Diving Operations Manual (U.S. Navy 1974b). Not only does it tell the operator what action to take depending on the state of the patient and his response to that action in the light of any special conditions prevailing, but it indicates what to do if the treatment fails. However, it does not cover all eventualities such as the worrying case of symptoms occurring at an appreciable depth.

A final word of caution in the prescribing of oxygen might be appropriate here in the event that some preliminary findings in this laboratory are substantiated. These imply that over-exposure to oxygen might impair the ability of the lung to filter out silent bubbles and so predispose

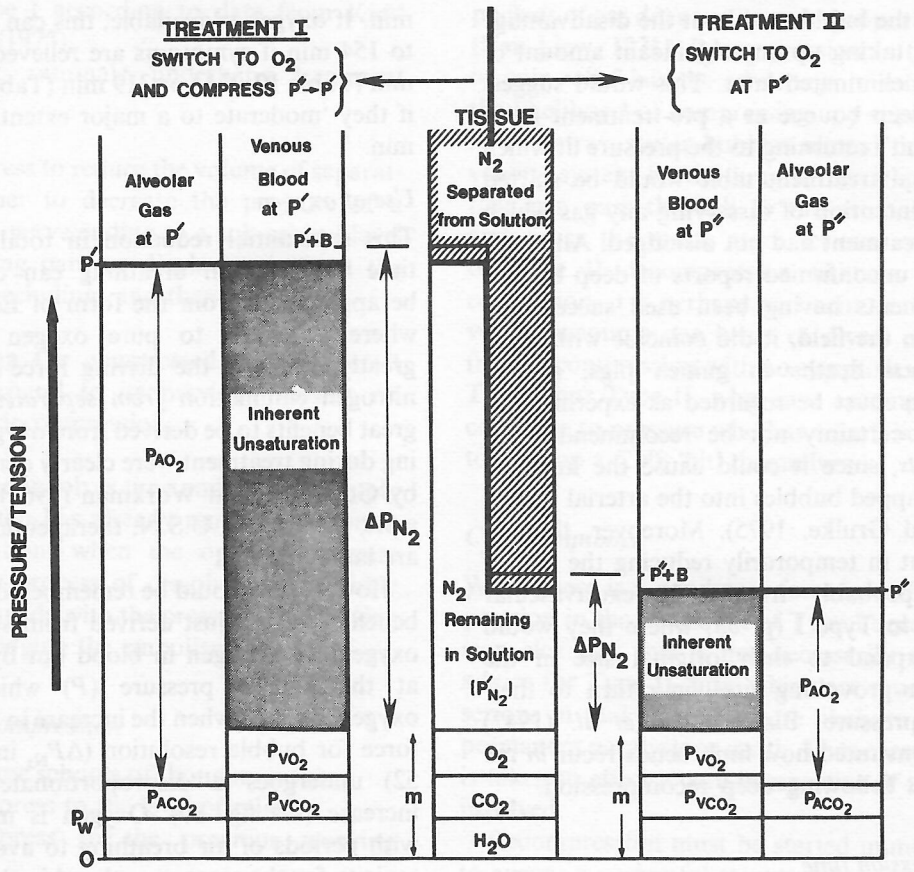

Fig. 80 Demonstrating how the inherent unsaturation and hence the driving force (ΔP_{N_2}) for resolving 'dumped' nitrogen is increased with switching to oxygen breathing (treatment II at pressure P''). It also shows how ΔP_{N_2} can be increased, and hence the treatment improved, by compressing from P'' to P' in addition to switching to oxygen (I)

the subject to a neurologic 'hit' (p. 68), particularly if recompression has a similar tendency (p. 230).

Bends at depth

The treatments depicted in Table 18 refer largely to decompression sickness presenting after return to the surface or during the last few stops. However, when symptoms occur deeper than 6 ATA or show no remission on recompression to this pressure, then much higher pressures must be used, Elliott (1967) quoting a case developing at 230 fsw which had to be returned to 450 fsw to be symptom-free. Recompression to such equivalent depths must naturally be performed using heliox which poses no particular problem unless the diver had already switched to air before onset. It is then better to recompress by adding helium to the breathing mix rather than substituting it for any of the nitrogen if this is technically feasible.

The propensity for vestibular symptoms to occur at depths in excess of 300 fsw and on switching to air at 120–180 fsw, has meant that with the high incidence of these category III symptoms during the recent spate of very deep diving, some knowledge of the treatment of these category III symptoms has started to accumulate. Thus Youngblood *et al.* (1975) recommend immediate recompression to 100

Table 19 U.S. Navy treatment of decompression sickness and air embolism (the Treatment Tables)

Depth (in feet)	Time in minutes at stop; breathing media: air/oxygen (A/X); elapsed time in {hours: minutes}							
	IA	IIA	III	IV	V	VI	VA	VIA
165		30 A {30}	30 A {0:30}	½ to 1½ hr. A {1:30}			15 A {15}	30 A {30}
165 to 60							4 A {19}	4 A {34}
140		12 A {43}	12 A {0:43}	½ hr. A {2:01}				
120		12 A {56}	12 A {0:56}	½ hr. A {2:32}				
100	30 A {30}	12 A {69}	12 A {1:09}	½ hr. A {3:03}				
80	12 A {43}	12 A {82}	12 A {1:22}	½ hr. A {3:34}				
60	30 A {74}	30 A {113}	30 X or A {1:53}	6 hr. A {9:35}	20 X {20}	20 X {20}	20 X {39}	20 X {54}
60					5 A {25}	5 A {25}	5 A {44}	5 A {50}
60					20 X {45}	20 X {45}	20 X {64}	20 X {79}
60						5 A {50}		5 A {84}
60						20 X {70}		20 X {104}
60						5 A {75}		5 A {109}
60 to 30					30 X {75}	30 X {105}	30 X {94}	30 X {139}
50	30 A {105}	30 A {144}	30 X or A {2:24}	6 hr. A {15:36}				
40	30 A {136}	30 A {175}	30 X or A {2:55}	6 hr. A {21:37}				
30	60 A {197}	120 A {296}	12 hr. A {14:56}	11 hr. A {32:38}	5 A {80}	15 A {120}	5 A {99}	15 A {154}
30				1 hr. X or A {33:38}	20 X {100}	60 X {180}	20 X {119}	60 X {214}
30					5 A {105}	15 A {195}	5 A {124}	15 A {229}
30						60 X {255}		60 X {289}
30 to 0					30 X {135}	30 X {285}	30 X {154}	30 X {319}
20	60 A {258}	120 A {417}	2 hr. A {16:57}	1 hr. A {34:39}				
20				1 hr. X or A {35:39}				
10	120 A {379}	240 A {658}	2 hr. A {18:58}	1 hr. A {36:40}				
10				1 hr. X or A {37:40}				
0	1 A {380}	1 A {659}	1 A {18:59}	1 X {37:41}				

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fsw deeper than the pressure at which they occurred.

Other treatments

The use of drugs has not proven of any appreciable benefit in the treatment of decompression sickness, although there are claims to the contrary, e.g. Saumarex *et al.* (1973). Generally they are limited to analgesics for the relief of bends pain. Heparin has been advocated by Barthelmy (1963) for its anticoagulant properties but it now appears that any benefit is more likely to be derived from its anti-lipaemic action (Philp *et al.*, 1967).

The most effective of the supplementary therapeutic measures is intravenous infusion of low-molecular-weight dextran which has even been found to cure a few cases which have failed to respond to recompression (Cockett and Nakamura, 1964). In their review of treatment procedures, Kidd and Elliott (1975) consider this measure to be more effective in cases where there has been some evidence of haemoconcentration. This would be compatible with the view that the pressure differential bending a nerve ending is derived not only from separated gas dumped in extravascular sites but also from a shift of fluid (p. 57). The higher colloid osmotic pressure provided by the dextran would tend to reverse this shift and so reduce the deforming pressure acting on the nerve ending but to a much lesser extent than recompression i.e. shifting out fluid to help accommodate the bubble in an extravascular site. However, the effect of intravenous infusion can be equally well interpreted on the basis that plasma expanders will tend to reverse blood disorders particularly increased blood viscosity (p. 51) and restore tissue perfusion. This explanation is compatible with its beneficial effect reported in a case of Type II decompression sickness (Barnard *et al.*, 1966). However this therapeutic measure should still be considered an adjunct to the much more effective treatment afforded by immediate recompression.