Chapter 4

Gas Separation

Whether bubble formation necessarily leads to bends is an issue discussed later (Chapter 6) but the evidence presented so far leaves little doubt that decompression sickness can be avoided if gas is prevented from separating from solution in the body. This has been the belief underlying almost all attempts to formulate safe decompression schedules; although whether they actually achieve this in practice is quite a different matter. Before taking up this question when describing preventive methods in Chapter 5, it would seem desirable to acquire more insight into the overall physics of bubble formation and allied phenomena.

The formation of a gas phase by decompression can involve as many as four distinct processes.

(1) Supersaturation of the solution: to some finite degree, although negligible levels may be adequate to initiate the next step in some systems.

(2) Nucleation: inception of the gas phase as minute specks (nuclei) if not already present.

(3) Growth: transfer of gas molecules from solution into the gaseous phase.

(4) Coalescence: or any other mechanical congregation of the gaseous phase separated from solution to produce a larger bubble or a larger accumulation of gas causing a greater local deformation of the medium.

Before discussing these steps in more detail, the simple case should be considered of a single gas in contact with its solution in water.

Solutions of gases

In Chapter 1, it was seen that the law governing the solution of gases is Henry's law (Equation 1). This states that a gas will tend to separate from solution, i.e. to pass from the liquid phase into the adjacent gaseous phase, if the tension of that gas exceeds its partial pressure in the gaseous phase; while it will tend to move in the opposite direction if this gradient is reversed. At least, this holds provided there *is* a stable gaseous phase into which the liquid phase can 'dump' the gas in true physical solution in excess of the quantity which it would contain at equilibrium, i.e. at the position of true saturation as described by Henry's law. If the inception of the gaseous phase is suppressed, then gas which remains in *true physical solution* in excess of saturation is said to be in supersaturated solution. Thus decompression provides one means of supersaturating a solution of a gas and providing a driving force for bubble growth.

The real problem in determining whether a gas will be 'dumped' from solution arises in deciding whether there is a stable gas phase present. The question is therefore one of determining the point at which local microregions of the gas phase (nuclei) are formed which are sufficiently stable to initiate the transfer process and whether such centres for bubble growth are present in tissue anyway.

Nucleation

If bubble growth is to be avoided altogether, and it is assumed that no stable gaseous micro-

regions are present prior to supersaturation, then it is necessary to ascertain the conditions under which nuclei are formed by decompression and how these may be best defined by the environmental parameters. Since almost all approaches to the calculation of conventional decompression tables are based on a critical limit to supersaturation (see Chapter 5), it is imperative that particular attention is paid to any evidence of a 'trigger point' or point of profuse nucleation for initiating gas deposition as bubbles—not only in gaseous cavitation but in other physical systems from which this concept was ensconced.

Suspended transformation

Delayed gas separation is just one example of a very common phenomenon in nature known as suspended transformation. This occurs when one or more parameters of any system are changed such that the formation of a new phase would enable that system to revert to a more stable thermodynamic configuration and yet, in the total absence of that phase, the transition is suppressed. Sometimes the system can remain in this metastable state almost indefinitely.

There are innumerable examples of suppressed transformation in the literature which include the following categories.

(1) Solid:solid transitions, where the appearance of a more stable polymorphic form may be delayed almost indefinitely, e.g. the delayed reversion of yellow to red phosphorus at normal room temperature. There are many examples in metallurgy but one of particular historical interest is the use of tin buttons on the uniforms of Napoleon's army. These were made from the malleable β form of this metal which is stable under normal conditions and is still unchanged at temperatures significantly below the 13·2 °C transition point for transformation to its α form (grey tin). However, with the extreme supercooling imposed by a Russian winter, the β-tin tended to revert to its more stable, yet powdery, α form—much to the embarrassment of the invading army.

Another group of solid:solid transitions of great commercial interest is crystallization in polymers (Price, 1969) where the formation of spherulites in nylon fibres, for instance, may greatly increase tensile strength. However, perhaps these systems should really be regarded as supercooled melts more akin to the glasses where nucleation considerations are, again, most important (Hammel, 1969).

(2) Liquid:liquid transitions, where the temperature may fall below the value at which two liquids are totally miscible and yet separation of the system into two liquid phases is delayed. A common example is a mixture of phenol and water.

(3) Solid-in-gas, such as the formation of ice crystals in a supercooled cloud. Much attention is being given to this problem (Boucher, 1969) in the hope of controlling weather patterns and avoiding natural disasters such as hurricanes by artificially 'seeding' clouds with silver iodide crystals—particularly effective as ice nuclei below -5 °C (Vonnegut, 1947).

Another example of the gas:solid transition of great commercial interest is the condensation of metal vapours on substrates suitably prepared to give the desired nucleation rate (Walton, 1969).

(4) Liquid-in-gas, such as the nucleation of clouds in air supersaturated with water vapour (Andres, 1969) and droplet formation from steam nozzles (Wegener and Mack, 1958). Perhaps the best laboratory example is provided by the piston cloud chamber of Wilson (1897) in which saturated air is rapidly expanded by decompression ($P_1 \rightarrow P_2$). Gradually increasing the expansion ratio, Wilson observed no condensation until a supersaturation ratio of 4·2 was reached. From this point until a ratio of about 8, a relatively small number of drops formed while, after 8, the vapour produced a fog of progressively smaller droplets. These results were interpreted as heterogeneous nucleation up to a supersaturation ratio of approximately 8 and homogeneous nucleation thereafter, giving a linear relationship between

$\log(P_1/P_2)$ and $T^{-3/2}$ for the same number of embryos (Powell, 1928). T is the absolute temperature. However, such relationships were found to apply to the suppression of droplet formation only if there are a few preliminary expansions of the chamber to 'wash out any ordinary nuclei' by causing condensation on any 'foreign particle' present which can then be precipitated. The Wilson cloud chamber has proved of great value in tracking nuclear particles as the trail of microdroplets which they nucleate *en passant*.

(5) Solid : liquid, including supercooling of a liquid melt, superheating of a solid above its melting point and supersaturation of a solution either by cooling or by solvent evaporation.

Since the latter was the first system to receive extensive attention, its selection for more detailed consideration provides a suitable introduction for the terminology and thinking on suppressed transformation. It is also particularly relevant historically for its antecedence to the Haldane approach to the diving tables (Chapter 5). However, before considering this last example of suppressed transformation in much greater detail, there are certain general facets of nucleation which should be mentioned since they apply to all of the cases cited above.

Heterogeneous nucleation

The generation of the supersaturated state may be a result of chemical or photochemical reaction, or the consequence of a change in temperature, pressure, tension or other chemical or physical condition. Domains of the new phase may then form around ions, impurity molecules, on dust particles or at structural singularities such as dislocations and other imperfections (Dunning, 1969). Such centres for growth are termed heterogeneous nuclei since they differ in composition from both the new and the parent phases.

Thermodynamic considerations

If these are not present, then the degree of supersaturation can be further increased with the solution becoming intrinsically more unstable. According to the classical theory of nucleation (Gibbs, 1906), this is best expressed as the difference (ΔG) in the Gibbs Free Energy and hence in the chemical potential of one molecule in the supersaturated state (μ_I) relative to its value in the bulk of the new phase ($\mu_{II\infty}$). Moreover, if the case is considered of formation of a nucleus within a supersaturated vapour of pressure p_I whose vapour pressure would be $p_{II\infty}$ at equilibrium at the same temperature, then

$$\Delta G = (\mu_I - \mu_{II\infty}) \propto \log(p_I/p_{II\infty}) \qquad (10)$$

From such simple thermodynamic considerations, it can be seen that the 'drive' to form the new phase increases very rapidly with the degree of supersaturation. This rapid rise in intrinsic instability is reflected in the sensitivity of the system to the slightest trace of foreign material. This is reflected, in turn, in the reproducibility of results which was such a problem to Fahrenheit (1724) that he even considered the freezing point of water to be variable and so avoided it when selecting his temperature scale in 1714.

The same heterogeneous nuclei tend to act in all systems. The writer has decompressed a supersaturated solution of Epsom's salts in contact with liquid paraffin to find a bubble growing in the oil attached to the liquid–liquid interface at the same point as a crystal is formed and is growing into the aqueous phase. Furthermore, there seems to be a critical degree of supersaturation at which each of these more marginal impurities appears to be activated into bubble formation. Thus, in any system not previously supersaturated to remove them, there seems to be a series of heterogeneous nuclei with a continuous spectrum of activation energies at which intrinsic instability becomes sufficient for them to initiate the new phase.

Homogeneous nucleation

When precautions are taken to 'use up' heterogeneous nuclei, or otherwise avoid them, then further supersaturation can occur but eventually leads to a state of sufficient instability that it breaks down and there is spontaneous

deposition of the new phase. This is attributed to the formation of minute specks of the new phase within the parent phase and, since their composition is the *same* as the bulk of the new phase eventually precipitated, this process is termed homogeneous nucleation.

Whereas heterogeneous nucleation becomes apparent for minimal supersaturation, many theoretical attempts have been made to relate homogeneous nucleation to the degree of supersaturation and hence to the physical parameters of the system. These tend to involve highly mathematical analyses (e.g. Dunning, 1969; Sigsbee, 1969). However, in qualitative terms, each seeks to describe the maximum aggregate of molecules, atoms or ions which can come together at any time and yet exceed the minimum size for stability. Before expounding current thinking any further, it may be as well to return to the simple case of crystallization to see not only how many of the present concepts were developed but how many of the older misconceptions arose.

Early work on nucleation

Much of the very early work on the crystallization of common salts must be discounted on account of the lack of precautions taken to exclude dust and consequently the unknown number of heterogeneous nuclei which it introduces. However, by the middle of the nineteenth century, biologists had become aware that the atmosphere contained all manner of micro-organisms—a concept soon applied to non-living particles and their ability to 'infect' supersaturated solutions with centres of growth (Schroder and von Dusch, 1854). Stringent efforts to reduce this 'infection' led to more meaningful results such as measurements of the time lag before crystallization occurred in solutions of known supersaturation (de Coppet, 1875).

The metastable limit

Studies like these then led Ostwald (1897, 1900) to propose two types of supersaturated solution:

(a) labile solutions which will crystallize in a short period of time due to spontaneous homogeneous nucleation; and

(b) metastable solutions which remain unchanged for apparently unlimited periods of time provided the solute concentration does not exceed a critical value above which they become labile. Ostwald termed this concentration threshold the *metastable limit* (see fig. 23).

Metastable and labile regions were also observed in the supercooling of melts (Tammann, 1898). Thus, at the turn of the century, when Haldane and his collaborators at the British Admiralty were formulating their now famous method for calculating diving tables, the metastable limit was then the accepted concept for describing the threshold at which supersaturated solutions became labile. Moreover, the work on cloud chambers *at that time* by Wilson (p. 77) had indicated that this metastable limit not only applied to droplet formation in gases but could be well described by the expansion ratio ($p_I/p_{II\,\infty}$) in Equation 10. This bears a remarkable resemblance to the Haldane 'decompression ratio' to be evaluated in much detail later (Chapter 5). Although no

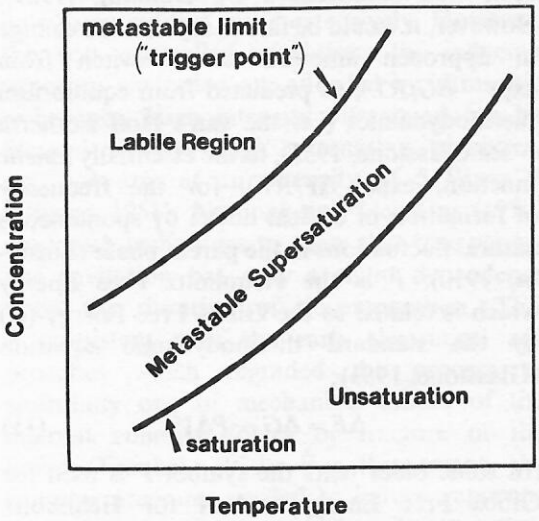

Fig. 23 Depicting the Ostwald concept of a metastable limit to supersaturation beyond which nucleation of the suppressed phase will occur. Ostwald's work referred largely to solutions of solids supersaturated by temperature change but the same concept can be applied to gas solutions supersaturated by decompression

reference was made to such contemporary work in the classical papers of Boycott *et al.* (1908), the expansion/decompression ratio as a description of a metastable limit to supersaturation involving gases certainly reflected scientific thinking on suppressed transformation at that time—or, at least, upon homogeneous nucleation.

'Classical' theory of nucleation

Although Miers and Isaac (1908) published further work at that time tending to confirm the existence of labile and metastable regions in describing crystallization, soon there were objections to the idea of any sharp change in the bulk properties of the solution at this limit (de Coppet, 1907; Tammann, 1926).

In 1926, Volmer and Weber recognized that the metastability of a supersaturated phase is more a question of kinetics; although intimations that time is significant in phase change can be found in earlier papers by Thomson (1859) and de Coppet (1875). Moreover, it led to a complete 'rethinking' of suppressed transformation. The full mathematical descriptions would occupy several chapters and have been well summarized by Dunning (1969). However, it would be fair to say that the change in approach amounts to a switch from $\exp(-\Delta G/RT)$, as predicted from equilibrium thermodynamics (i.e. the van't Hoff isotherm —see Glasstone, 1953), to the essentially *kinetic* function, $\exp(-\Delta F/RT)$, for the frequency of formation of critical nuclei by spontaneous natural fluctuations in the parent phase (Einstein, 1910). F is the Helmholtz Free Energy which is related to the Gibbs Free Energy (G) by the standard thermodynamic equation (Glasstone, 1953):

$$\Delta F = \Delta G - P\Delta V \qquad (11)$$

(In some older texts the symbol F is used for Gibbs Free Energy and A for Helmholtz Free Energy.)

In Equation 10, it is seen that the expansion ratio ($p_I/p_{II\infty}$) describing the metastable limit to supersaturation of a gas by vapour should be constant since ΔG was constant. However, in changing to the kinetic approach, Equation 11 shows that ΔF is dependent upon P and V and hence the probability of forming homogeneous nuclei, $\exp(-\Delta F/RT)$, is markedly dependent on the degree of supersaturation.

This also applies to cavitation by decompression, since ΔF refers to the difference between the supersaturated state and the equilibrated state, i.e. the state *after* growth of the gas phase and hence *after* volume change (ΔV) of the solution. Thus 'classical' nucleation theory predicts no fixed metastable limit to supersaturation, or fixed threshold to the labile zone but rather a continuous increase in the probability of nucleating with further decompression. Even so, there should still be a zone of more rapid increase in this probability with respect to expansion ratio (see fig. 24).

Statistical mechanics

An alternative to this 'classical' theory associated with the names of Volmer, Weber, Farkas, Becker, Döring and Zeldovich has been the

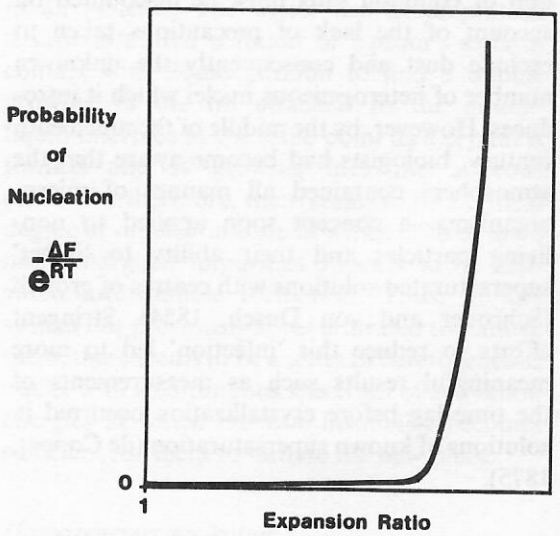

Fig. 24 The likelihood of forming liquid droplets plotted as a function of the expansion of its vapour. The region of fairly sharp increase in the probability has been compared with Ostwald's metastable limit to supersaturation. Data from Dunning (1969)

direct use of statistical mechanics to predict the nucleation probability function. This has developed largely from the Mayer (1937) theory of condensation and although it may be aesthetically more satisfying to theoretical physicists than the Gibbs criterion for stability, it leads to probability distributions which differ little from those developed by the 'classical' theory.

All of the disciplines associated with the many examples of suppressed transformation cited at the beginning of this chapter have now followed one or other of these approaches, or a combination, and it is only in decompression sickness that anyone still adheres to the original Ostwald concept of a critical limit to supersaturation, i.e. a fixed 'trigger point'.

However, before discussing the particular case of solutions of gases in more detail, mention should be made of some other general characteristics of supersaturated solutions.

Behaviour of supersaturated solutions

Ostwald (1897) showed that no more than 10^{-10} g of NaCl is enough to seed its supersaturated solution in water, while these solutions could also be seeded by various contaminants as already described under heterogeneous nucleation. Various mechanical means can also initiate precipitation such as shaking, scratching, rubbing (Gay-Lussac, 1819) and intense sonic radiation (Vanhook, 1969). In fact, in their studies of the effects of mechanical stimulus on crystallization, Young (1911) and Young and van Sicklen (1913) found that they could induce nucleation anywhere within Ostwald's hypothetical 'metastable zone' if they supplied the appropriate amount of mechanical energy. Hence they concluded that the whole supersaturated region was effectively labile (fig. 23).

The tendency to nucleate is less if the parent phase is retained in smaller vessels. In very early studies of suppressed transformation, it was found that water could undergo more 'under-cooling' if transferred to capillary tubes (Despretz, 1837) or when dispersed as smaller droplets in immiscible liquids of equal density (Dufour, 1863). This scale effect has been attributed to the isolation of foreign particles in individual drops leaving the others free of heterogeneous nuclei (Turnbull, 1949). It also raises the question of the effective 'vessel size' for bubble formation in tissue (see p. 252). However, more general aspects of gaseous cavitation *per se* should first be considered.

Bubble Inception

As early as 1819, Gay-Lussac showed that supersaturation also applied to solutions of gases, such as carbon dioxide in water; and Berthelot (1850) investigated the formation of vapour bubbles in 'overexpanded' liquids. These early examples of nucleation help to demonstrate the two basically different types of cavitation—vaporous and gaseous.

Vaporous cavitation

Strasberg (1956) restricts vaporous cavitation to cases where the nucleus grows explosively and contains predominantly vapour. Violent mechanical actions such as those associated with a ship's propeller or liquid pumping are capable of inducing this type of nucleation and have been studied quite extensively. However, the best controlled conditions for inducing vaporous cavitation are afforded by ultrasonic techniques. High intensity ultrasound can be focused to give high alternating pressures, e.g. ± 4 atm at an intensity of 5 $W.cm^{-2}$ (Hueter, 1951). Noltingk and Neppiras (1950) used such techniques to show that true vaporous cavitation has only a slight dependence upon the duration of decompression. This is consistent with the early theoretical approaches which regraded the process as essentially one of mechanical failure of the internal cohesive forces or fracture of the liquid (Frenkel, 1939). For this reason the negative pressures needed to induce vaporous cavitation are often termed 'tensile strengths'.

Abreast of approaches to other aspects of suppressed transformation, these early theoretical treatments were superseded by those of a more statistical nature with Fürth (1941)

basing his analysis upon the distribution of 'holes' in liquids and the likelihood of their congregating into a stable nucleus. Circumventing their massive mathematical derivations, these 'hole theories' essentially predict a labile region and another, roughly corresponding to the old metastable range, in which there is a graded probability of nucleation occurring depending upon the extent of supersaturation.

Tensile strengths of liquids

The various theoretical approaches have produced estimates of tensile strengths for degassed water ranging from the vapour pressure to 350 atm negative pressure (Knapp, 1952; Hemmingsen, 1970; Apfel, 1970a, b, 1972). It must be remembered that negative pressures, far exceeding any possible vacuum, are perfectly feasible in a solid or liquid in which there is no cavitation.

Fracture of a gas-free liquid can be induced in practice not only by reducing the absolute pressure (decompression) but also by elevating the vapour pressure. In the latter case, Kenrick *et al.* (1924a) were able to superheat water to 270 °C in small clean capillaries at atmospheric pressure, the vapour pressure at this temperature being 54 ATA.

The alternative method of supersaturating by decompression has enabled some remarkable negative pressures to be recorded under both static and dynamic conditions by a wide variety of methods. A list of values and their source of reference is given in Table 6.

The values for these 'tensile strengths' of liquids cited in Table 6, particularly the higher values, are often quoted in support of critical supersaturation theories of decompression sickness. However, the enormous variation of these values needs no comment. Moreover, most contributors to this list tend to emphasize their highest reading, often not recording other runs failing to reach the maximum. While this approach would seem quite justifiable in its avowed intention to determine the fracture strengths of liquids, such data is much less acceptable in assessing the likelihood of *failure* of the system. Such data would therefore seem of little use in deciding whether the metastable limit exists or not but the subject is mentioned here since references to such values abound in the literature on decompression sickness.

Relevance in biological systems

A possible exception to this last statement occurs in plants, the microstructure of which

Table 6 Recorded tensile strengths* of various liquids

Tensile strength (ATS)	Liquid	Reference	Method
300	water	Bethelot (1850)*	static
4·8	water	Reynolds (1878)	dynamic
30	water	Meyer–Breslav (1911)	static
40	ether	Meyer–Breslav (1911)	static
150	water	Dixon (1914)	static
207	cell sap	Dixon (1914)	static
2·38	water	Vincent (1941)	static
2·94	mineral oil	Vincent (1941)	static
2·9–114	mineral oil	Vincent (1941)	static
100–1000	water	Harvey *et al.* (1944a)	static
0·8	water	Dean (1944)	dynamic
100–200	water	Pease and Blinks (1947)	static
280	water (10 °C)	Briggs (1947)	dynamic
20	water	Willard (1953)	ultrasonic
200	water	Galloway (1954)	ultrasonic
140	benzene	Galloway (1954)	ultrasonic

*Quoted and checked by Meyer and Dixon using the same method.

has developed without direct contact with the atmosphere in much the same way as mammalian tissue. The tensile strength of liquids represents a subject of great importance in studying the physiology of trees where enormous negative hydrostatic pressures must exist without cavitation in the very fine channels available for the flow of cell sap. Of particular interest is the mangrove tree which needs to overcome the large osmotic pressure of the sea (25 ATA) in extracting fresh water into its root system (Scholander *et al.*, 1964).

These values are all the more interesting when one remembers that *gases* are present, so that this indicates a very effective system for avoiding gaseous rather than vaporous cavitation. However, the turgor of trees is very different to that of mammalian tissue. After all, trees have evolved to withstand these enormous negative pressures whereas, under normobaric conditions, there is no such need in man who has *positive* pressure (relative to ambient) in all vessels and other fluid systems of his body.

This argument implies that the first formation of bubbles in a subject could require a different supersaturation threshold to subsequent attempts. In this connection, it has been the writer's experience that a new 'diving' goat will usually 'bend' for the first time for a decompression differing widely from its subsequent norm.

However, before looking at the immensely complex phase structure of body fluids and the multiplicity of tissue liquid compartments as a cavitation medium, gaseous cavitation in pure liquids should first be considered.

Gaseous cavitation

There is unanimous agreement that the likelihood of cavitating a liquid by decompression increases with its gas content (Hueter, 1951), true vaporous cavitation representing one point at the lowest end of the probability distribution. Coakley (1971) has demonstrated that an acoustic intensity of 142 $W.cm^{-2}$ was sufficient to produce the first indication of stable bubbles at the focal point in air-saturated water, while 175 $W.cm^{-2}$ produced visible bubbles of up to 300 μm diameter. Gas is considered to enter these ultrasonically induced nuclei by rectified diffusion (Plesset, 1963; Apfel, 1970a, b). Other novel means of initiating bubble formation are provided by Reynold's cavitation, as seen in the type of vortex formation which can develop as a result of turbulent flow (Dean, 1944), and by tribonucleation.

Hayward (1967) has observed bubble tribonucleation in nucleus-free liquids under negative pressure in a hydrostatic tension monometer, the effect occurring with very gentle rubbing of the liquid–solid combination tested. Ikels (1969), on the other hand, devised a series of experiments to observe the effects of viscosity, velocity and gas solubility on nucleation and bubble formation due to a small ball rolling down the side of a test tube at reduced pressure. He concluded that increased viscosity facilitated bubble production. In addition, the decompression required for bubble formation was found to be in proportion to the product of the viscosity of the fluid and the velocity of the rolling ball and inversely proportional to gas solubility (Hemmingsen, 1970).

Hayward suggests that the tribonucleation phenomenon is probably not due to frictional heating since two spheres of air-free ice vigorously rubbed together will form nuclei. Rather the phenomenon is more likely to result from rapid separation of the solid surfaces leaving a momentary cavity (Harvey, 1951a). Campbell (1968) adds that tribonucleation and bubble growth are theoretically facilitated when the solid surfaces involved present a large contact angle.

Returning to the problem of gaseous cavitation simply induced by reducing the overall hydrostatic pressure, the probability distribution of activating nuclei into growth is very difficult to determine due to the enormous random scatter. However, averaging twenty decompressions to obtain each point and taking thirty points, there appears to be a linear relationship between the air content of water and its 'critical inception pressure' as measured by ultrasonic techniques (Strasberg, 1956). By extrapolating these results and those of Blake (1949) to a system at normobaric condi-

tions, the air tension would be 1·65 atm, corresponding to a decompression ratio of 1·65. However, this is just a projected mean, so that on many occasions gas separation would be expected for much lower values.

Random scatter

The magnitude of the scatter can be appreciated from the work of Crump (1949) who records his data for pumping both fresh and sea water through a Venturi nozzle. His graphical presentation of several hundred results, on the basis of air content *versus* critical inception pressure, indicates that gaseous cavitation is a very random process indeed. For sea water, at least, there is an appreciable probability of nucleation occurring for decompression of less than 90 mm Hg (4 fsw). Crump also found that the critical inception pressure dropped markedly with increasing temperature, so that this threshold would be even lower at body temperature (37 °C).

It would be quite justifiable, however, to argue that the threshold decompression for sea water need not apply *in vivo* where the cavitation medium can be regarded as sealed from the environment. In support of this point, evidence has already been presented from other sealed biological systems such as the mangrove tree (p. 83), not to mention the maximum 'tensile strengths' recorded for cell sap (Table 6).

Pressure 'memory' of solutions

Reasoning such as this has led many workers to go to the other extreme and work with 'denucleated' solutions to try to ascertain the decompression threshold for bubble formation. Several methods have been employed in attempting to achieve this ideal state, including the application of hydrostatic pressure and the chemical generation of carbon dioxide by mixing ultracentrifuged molar solutions of $NaHCO_3$ and HCl (Harvey, 1951a). Mixing these solutions at normal pressure did produce a few bubbles.

Bubble formation by decompression, however, can be very effectively suppressed by previous application of extreme hydrostatic pressure to the solution without permitting further gas to dissolve. Techniques for the compression of solutions isolated from the gas phase have been described by Pease and Blinks (1947), Harvey (1951a) finding 30 min at 16,000 psi to be most effective. With such pretreatments, water saturated with oxygen, nitrogen or carbon dioxide at 100 ATA could be decompressed to normal atmospheric pressure without bubbling (Kenrick *et al.*, 1924b), while this could be achieved with saturation at 250 ATA, even with carbon dioxide but not on all occasions (Clare, 1925). Strasberg (1956) has attempted to quantify this 'memory' of the solution for its pressure history by the expression

$$P_c = i_1 . p - i_2 . P_u \qquad (12)$$

where P_c is the critical pressure for cavitation, p is the gas tension and P_u is the maximum hydrostatic pressure to which the solution has been subjected, while i_1 and i_2 are constants where $i_1 > i_2$.

Actually, the tension of a gas (p) does not remain constant when its solution is compressed in isolation from the gaseous phase. There is a slight increase amounting to some 760–860 mm Hg air in water for compression from 1.0 to 1000 ATA (Enns *et al.*, 1965)—a rather larger increase (Δp) than predicted from the standard equation of Poynting (1896a, b):

$$\Delta p . V = \Delta V . P_u \qquad (13)$$

where ΔV is the change in the solution volume (V) for a hydrostatic compression P_u.

Most authors attribute the 'memory' of the

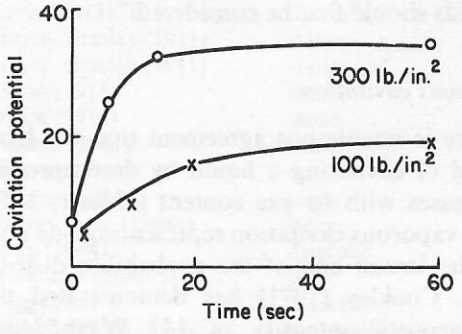

Fig. 25 The potential required to produce cavitation by ultrasonic means at various times after the application of hydrostatic pressure *per se*. Increasing potential reflects increasing difficulty in inducing cavitation. Data from Iyengar and Richardson (1958)

gas solution for hydrostatic pressure to the presence of undissolved nuclei in normal liquids (Harvey, 1951a; Willard, 1953). Thus compression tends to reduce them to a point where they can no longer initiate growth of the gaseous phase upon subsequent decompresson of the solution to a supersaturated state. This probably involves dissolving them either totally or in part, since this de-activation process is not only more effective at higher hydrostatic pressures but is dependent on the time that these pressures are applied (see fig. 25).

Gas nuclei

These observations leave little doubt that, in normal liquids, there are gas nuclei present analogous to those postulated in the other aspects of suppressed transformation described earlier. However, their formation or activation by decompression is still poorly understood. The literature is particularly mathematical and confusing and leaves this writer with the impression that, if the physicists cannot agree on the mechanism in pure liquids, then what hope have physiologists of discovering the truth about bubble inception in media as complex as body tissues?

However, there are several broad areas of agreement in theoretical treatments which warrant mention before resorting to direct experimental testing *in vivo* to try to answer the questions relevant to decompression sickness. Firstly, there is a need for a certain minimum energy concentration to form the nucleus—akin to the activation energy of a chemical reaction (Ross, 1938) and hence consistent with the kinetic approach adopted in the 'classical' theory of nucleation already outlined. This energy barrier can be overcome either by the chance concentration of energy as predicted by the Boltzmann distribution of molecular energies or by the supply of discrete high-intensity 'packages' in such form as the products of radioactive decay.

The first approach is essentially statistical and leads to a probability distribution for the formation of nuclei resembling that for droplet nucleation shown in fig. 24. Thus, for any degree of supersaturation, there is a finite chance of forming nuclei.

Nucleation by isotope decay

On the other hand, supply of the activation energy in the form of cosmic radiation or the fission products of radioactive isotopes should lead to a more random distribution. Evans and Walder (1974) have postulated this as a major source of bubble inception in caisson workers, pointing out that the number of disintegrations of U^{235} in the body coincides with the bends incidence. However, this would imply that the incidence of decompression sickness was independent of the decompression profile provided there was supersaturation. Although the decay of radioisotopes or cosmic radiation is therefore most unlikely to be the primary source of bends it could be a factor contributing to the 'normal' level of nuclei present in tissue. Whether such a 'reservoir' of nuclei is normally present in the body is a key factor in the fundamental design of decompression procedures.

On the subject of charged particles, ions present in the air supply to buildings can affect health (Krueger and Reed, 1976) and, if concentrated in the gas supply system to divers, could influence the outcome of decompression.

Critical size of nucleus

Before pursuing this controversial issue any further for the moment, it is necessary to return to the second point which is common to the major theories of bubble nucleation. This is their universal shortcoming in needing to specify a critical radius for the nucleus in deciding whether its predicted energy configuration is likely to be stable. Reverting to simple equilibrium considerations, a bubble will tend to grow if the total gas tension (Σp) of the adjacent solution exceeds the total pressure of gas within the bubble, i.e. if

$$\Sigma p > P + 2\gamma/r_b + \delta_g = P + B \qquad (14)$$

where P is the absolute hydrostatic pressure of the solution, γ is the surface tension, r_b is the bubble radius and δ_g is the pressure required to overcome any elastic forces within the medium tending to oppose its deformation by the bubble. Thus δ_g is zero in a normal liquid. The excess bubble pressure for phase equilibrium (B) is the sum of δ_g and the term, $2\gamma/r_b$,

arising by virtue of curvature of the interface in accordance with the Laplace equation. This addition of mechanical factors is depicted in fig. 26.

It can be seen that B will decrease as the bubble grows ($r_b\uparrow$) until the interfacial factor becomes negligible. γ is small (of the order of 50 dyne. cm^{-1} for plasma) and may be reduced still further by surfactants or the 'organic skin' predicted to stabilize nuclei and believed by some to be present even in the cleanest liquids available (Fox and Herzfeld, 1954). Even so, B should become a very large term as r_b becomes very small, amounting to about 0·7 kg. cm^{-2} (535 mm Hg) for $r_b = 1.42$ μm. This value was estimated for water at 20°C (Dean, 1944). Hence much greater degrees of supersaturation, $(\Sigma p - P)$, are necessary to balance Equation 14 as smaller bubbles are envisaged. At some point a bubble becomes a nucleus and vice versa, so that this elementary reasoning based on the thermodynamics of macro-systems suggests that the critical degree of supersaturation for bubble inception is hyperdependent upon the diameter selected for the nucleus at inception (see fig. 26).

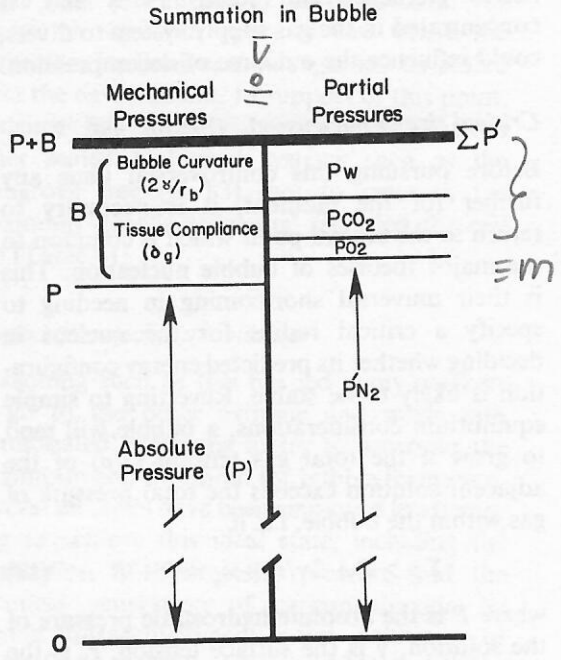

Fig. 26 Demonstrating the application of Dalton's law to gas bubbles *in vivo*. The sum of the mechanical factors contributing to the total hydrostatic pressure of the gas within the bubble must equal the sum of the partial pressures of the component gases

However, there is obviously a point of breakdown in this line of deduction, since a bubble is essentially unstable; it must either grow if its radius exceeds a value which balances Equation 14 or it must shrink it is less than this critical value for metastability. If it shrinks, then B might be expected to reach an enormous value until the bubble is crushed and totally dissolved. Yet, in practice, nuclei appear to survive—unless dissolved by the application of hydrostatic pressures which although high, e.g. 1000 ATA, are still small by comparison with $2\gamma/r_b$ as r_b approaches intermolecular dimensions.

This emphasizes the need to switch to thermodynamics and kinetics more appropriate to micro-systems in considering nucleation but it also raises the question of whether there is any other factor which could be stabilizing these microscopic nuclei against the enormous crushing pressures predicted by $2\gamma/r_b$. Even on the basis of statistical thermodynamics, there should be the same probability of the requisite number of gas molecules coming together at any one instant to form a nucleus whether the solution has been pretreated with extreme hydrostatic pressure or not. Accordingly, some other factor must be sought which could be tending to stabilize microbubbles against their intrinsic crushing pressures and so preserving the 'reservoir of nuclei' needed to explain solution 'memory'.

Bubbles in elastomers

A possible stabilizing factor for nuclei is provided if one follows the lead of several workers in the field of decompression sickness in preferring to study solutions *in vitro* which have mechanical properties more akin to those of gross samples of tissue. While gelatin solutions have proved popular for this purpose (LeMessurier, 1972; Strauss, 1974), their deformation produces a mechanical reaction which is a complex mixture of elastic and plastic forces. In other words, there is creep, a comprehensive analysis of the visco-elastic forces having

been undertaken by Yang and Liang (1972). Such complicating factors are largely avoided in simple elastic polymers such as the very soft siloxane rubbers.

Gent and Tomkins (1969) have shown that micro-cavities can be stabilized against appreciable external crushing pressures even in elastomers with relatively low shear moduli. Moreover these same nuclei can be activated into centres for bubble growth by minimal degrees of supersaturation.

This work is particularly interesting in view of the similarities between tissue and the elastomers used by Gent and Tomkins; these factors have been discussed by Vann and Clark (1975). This approach can therefore provide some scientific justification for the concept of a stabilized 'reservoir of nuclei' *in vivo*, although it may still not interpret the pressure 'memory' of pure liquids.

Reservoir of nuclei

Direct evidence for the 'reservoir of nuclei' *in vivo* has been provided by looking for bubbles in living translucent creatures after decompression. Gooden (1973) used the tail of the tadpole, while Evans and Walder (1969) found shrimp to be an ideal incompressible invertebrate with a definite 'memory' for applied hydrostatic pressure. They found that the number of bubbles observed increases with the degree of supersaturation in creatures not pre-pressurized and that decompressions of no more than several feet of sea water were sufficient to initiate the first bubbles. This threshold in shrimps has been studied by Beckman (personal communication) and found to be compatible with the inherent gas unsaturation of normal tissue as discussed in more detail later (p. 239).

Implications for acclimatization

Evans and Walder found a wide distribution in the degrees of supersaturation needed to provoke the various nuclei of the 'reservoir' into bubble growth. They point out that this supports their hypothesis that acclimatization to compressed air exposure is due to the 'using up' of the more readily activated nuclei on the early decompressions. The great advantage of this approach is that it offers an explanation for the indication that adaptation to one working pressure does not offer significant protection against decompression sickness following subsequent exposure to a higher pressure (p. 40).

Attractive as this hypothesis may be, it assumes that nuclei are 'used up' by their activation into bubbles *in vivo* in the same way that heterogeneous nuclei can be precipitated by preliminary expansions of a Wilson cloud chamber (p. 78). However, this writer feels that a 'treated' bubble is likely to leave larger and more nuclei rather than fewer, in the confined compartment or thixotropic body fluid in which it is captive in extravascular tissue. Thus, this hypothesis would be much more plausible if the limb bends from which the acclimatization data (see p. 40) were gathered were caused by *intravascular* bubbles, in which form the more readily activated nuclei could be removed from blood at the lungs—a major issue discussed on p. 66.

An ideal medium for keeping the bubbles captive while studying their formation *in vitro* and the nucleation spectrum in general is provided by gelatin solutions.

Gas separation in gels

A comprehensive description of the preparation of gelatin solutions and their use in studying gaseous cavitation induced by decompression has been compiled by LeMessurier (1972). This work largely describes modes of growth and will be discussed later but leaves little doubt that bubbles are much more difficult to initiate than in water, while 20% gelatin is much more difficult to nucleate than 10% (Harvey, 1951b) and usually requires seeding if one simply applies a vacuum to the stiffer gels equilibrated with room air. More recent studies (Strauss, 1974; Yount and Strauss, 1976) have sought to determine the threshold for nucleation, i.e. the all-important value for B in Equation 14.

The results of these investigations indicate that pre-existing nuclei account for at least 99·9% of the bubbles formed by decompressing gelatin of which 94% are already present in the water before the gel is prepared. It could be

argued that these findings are not relevant to the body because biological fluids are formed in a sealed environment but their studies of serum and egg albumin also reveal pre-existing nuclei.

Different nuclei become activated into bubble formation for different degrees of supersaturation, i.e. growth is initiated for different values of $(\Sigma p - P)$ in Equation 14 (see fig. 29). Hence Yount and Strauss attribute this to a distribution in sizes of the nuclei present, i.e. in r_b values needed to balance Equation 14. Thus it would seem fair to say that there *is* a 'reservoir' of nuclei normally present in solutions of gelatin but that these have a wide spectrum of degrees of supersaturation for their activation into supporting stable growth of the gaseous phase.

As in pure liquids, gas nuclei can be deactivated in gelatin by the application of very high hydrostatic pressure, presumably due to crushing (Yount and Strauss, 1976). When such denucleated gels are decompressed, much higher degrees of supersaturation are then needed to induce bubble formation by subsequent decompression, i.e. B values are much higher. Once again, however, it raises the question of the relevancy of denucleated solutions; can a solution which has been exposed to a very high hydrostatic pressure in the absence of the gaseous phase be compared with tissue which has not exceeded the 'bottom' pressure of a dive?

Tissue and gelatin solution may appear to have similar overall mechanical properties but on the micro-level they are very different. The distensible and elastic nature of most tissues is imparted by their membranous microstructure common to all living matter, each micro-compartment actually containing fluid. Even cytoplasm is liquid *at body temperature*. Hence B values for these fluids should be lower than for gelatin unless the membranes are restraining the bubble but such forces would not then become significant until *after* there had been appreciable growth and consequently well after a nucleus had been activated into a stable gaseous phase.

Another basic difference from the situation encountered *in vivo* is that the *in vitro* systems discussed so far all refer to cavitation in a homogeneous medium, whereas the body has two primary solvents for gases—one lipid and the other aqueous in nature, the two being immiscible with each other and yet widely interspersed in many tissues.

Heterogeneous systems

If the cork is released from a bottle of soda water, it is most unlikely that any bubbles will be seen to form anywhere other than on the glass walls. There are very few instances in which bubbles have been observed to form *de novo* in the bulk of the fluid. The only cases seem to arise with extreme decompression at virtually explosive rates as recorded by Clare (1925) and, even under these conditions, Briggs (1950) could not be certain of the nucleation site. The other means of generating bubbles within the bulk of the fluid is provided by the focusing of intense ultrasonic radiation.

Simply using non-explosive decompression, Wismer (1922) reported that all bubbles are formed in liquids at the retaining walls, while Pease and Blinks (1947) found it impossible to form bubbles in the bulk of the fluid. They concluded that a solid surface was needed as the point for gas separation from solution. The theoretical implications of the microgeometry of container walls has been discussed in great detail by Fisher (1948) and Harvey (1951a).

However, the simple explanation that the vessel walls retain small pockets of gas which act as the embryos for bubble growth no longer seems adequate. Farncombe (1925) has reported bubbles forming at the surface of solids deposited from the same solution as the gas. Moreover, it also applies to precipitated solids which are only wetted with difficulty by the solvent, i.e. those with contact angles exceeding the 90° level considered critical in many theories of surface nucleation. Furthermore, the surface need not be solid. This writer has found preferred bubble formation on human fat deposited from its solution in acetone by adding water in the absence of the gaseous phase. This observation can be interpreted on the basis that the freshly

formed lipid–aqueous interface has an affinity for pre-existing nuclei circulating in either liquid phase. However, such an interface would not possess the mechanical rigidity needed to stabilize nuclei by the 'crack' theories of bubble formation. This does not disprove these theories in their own context but it does detract from the emphasis placed upon the concept of tissue as a sealed system free from vessel-wall nuclei and therefore capable of withstanding appreciably more supersaturation than other gas solutions without cavitating.

Whatever the mechanism of nucleation, the nature of the interface is important. Harvey (1951a) records that a paraffin surface always bubbles profusely in soda water however well it is cleaned. This emphasis on the hydrophobic nature of the retaining boundary is particularly pertinent to all biological material which is immensely membranous down to the most microscopic tissue component—and the structural basis of these membranes is a bimolecular layer of lipid (Davson, 1964). At first sight this might appear to offer an enormous hydrophobic surface inducive to cavitation in all cells and sub-compartments but the lipoprotein molecules are considered to be orientated with their polar protein ends facing outwards on both sides of the membrane to present more hydrophylic surfaces in uninjured tissue.

Liquid–liquid systems However, the propensity for lipid inclusions in many cells and the high solubility of gases in these fat droplets, has aroused some interest in cavitation at the interface between aqueous and hydrophobic liquid phases (Hills, 1967a). These studies show that when bubble formation occurs in oil–water systems, it invariably does so at this interface. The appearance of bubbles is random so that, on any given occasion, one cannot predict whether they will appear or not. When they form, they become visible within a minute or so of decompression and few develop later. This is compatible with the concept of a pre-existing 'reservoir of nuclei' advanced earlier for single liquids and is again similar in so far as an increase in the degree of supersaturation produces more bubbles.

However, the absolute level of supersaturation needed to produce bubbles at the water–oil interface in the same numbers was appreciably lower and sometimes negligible—often less than two feet of sea water. This raises the question of whether the interface itself can initiate bubble inception or whether it simply facilitates the activation of nuclei attracted to it from the reservoirs normally present in each phase. The latter explanation seems more likely, since fine interspersion of the two phases to create 10–100fold larger interfacial area did not produce significantly more bubbles (Hills, 1967a). This indicates that a fat surface promotes activation of a wider range of the size spectrum of nuclei in the reservoir for a given degree of supersaturation.

These studies also showed that bubble formation at the liquid–liquid interface was dependent upon the solubility of the gas. One would naturally expect larger bubbles but a lesser degree of supersaturation (smaller B value) was needed to produce the same average number of bubbles of the more soluble gas.

Many of these findings were confirmed by Evans and Walder (1969) who went on to show that, in common with the single-phase systems already discussed, the liquid–liquid interface has a 'memory' for hydrostatic pressure (800 kg. cm^{-2}). This largely confirms that there is also a reservoir of nuclei in two-phase systems.

Summary

This review of nucleation has tended to avoid more than a mention of the standard theoretical treatments because not only do these require significant mathematical description to be appreciated but most are directed towards pure denucleated liquids under idealized conditions. However, even these yield a probability distribution of nucleation rather than a fixed threshold as assumed in the decompression ratio of Haldane and co-workers used to compute diving tables (p. 110). Their implied 'trigger point' conforms with other descriptions of the concept of the metastable limit popular at the turn of the century but subsequently abandoned in other disciplines. Even so, there is a fairly steep rise in the predicted probability

curves over a relatively narrow range of supersaturation which could be construed as a 'trigger range' *for the dissolved gas as a whole.* This immediately raises again the question of whether the first appearance of bubbles in the critical tissue(s) or the point of appreciable nucleation should be considered.

Looking purely at experimental results, there is no doubt that bubble formation can be suppressed in gas solutions with very high degrees of supersaturation by previously subjecting them to very high hydrostatic pressures in very clean vessels with hydrophylic walls. However, divers are not exposed to these extreme hydrostatic pressures in practice and any attempt to do so in the gas-breathing diver is likely to cause much more trouble due to the increased gas uptake. It is tempting to speculate here about liquid breathing (p. 209) to denucleate the diver under the better-controlled conditions in which he finds himself pre-dive or pre-decompression. Moreover, in passing from these idealized solutions towards a more biological situation by considering hydrophobic surfaces, less rigid gels, lipid inclusions and non-denucleated solutions, the distribution curve is shifted towards lower and lower degrees of supersaturation; and the work on shrimp indicates that tissue is no exception to this trend.

In conclusion, it is this writer's opinion that current knowledge of nucleation in the physical sciences would predict that bubble inception is random and will occur very readily in tissue. This really 'puts the ball back in the court' of the physiologists to decide whether:

(1) Only *one micro-region* of tissue needs to activate nuclei for sufficient growth to lead to bends, when theory would show that this occurrence should be random and with so many possible sites within any one tissue the probability of bubble growth would be appreciable for any condition exceeding zero-supersaturation; or

(2) bends are determined by the *average* micro-region of tissue. when the degree of supersaturation for the steeper increase in probability of nucleation would become a more relevant description and come closer to the concept of a 'trigger point' or metastable limit.

Hence it would be fair to conclude that nucleation theory is compatible with a fairly broad 'trigger point' if the overall bubble population of a tissue is relevant in determining bends but it is also compatible with virtually no metastable limit (zero-supersaturation) if the worst micro-region determines the imminence of symptoms. However, before taking this argument further, it is desirable to know how such average *or* local sites will permit these freshly activated gas nuclei to grow into bubbles.

Bubble Growth

Once established, a stable gaseous phase will grow by acquiring gas from its adjacent supersaturated solution. Unlike nucleation, the growth of a bubble is governed by physical laws which are well established and capable of exact mathematical description. This difference arises largely from the transition from a micro- to a macro- system as gas passes out of solution, so that it is then sufficient to apply standard rather than statistical thermodynamics and kinetics in analysing growth. Before considering the complex case probably encountered *in vivo*, of growth of a random distribution of nuclei, there are a few basic features to be considered first.

The interface

At one time it was believed that the interface *per se* between two phases represented a resistance to the transfer of solutes which was described quantitatively by an 'invasion coefficient' (Bohr, 1899; Krogh, 1918). However, it is now well established that phase boundaries offer no intrinsic resistance but that transfer is limited purely by diffusion or convection of the solute within the adjacent films of the two phases. This is expressed in the universally accepted 'two-film' theory of Whitman (1923)

which actually assumes equilibrium between the two phases at their points of contact in calculating solute transfer.

Convection

If one of the phases is in motion, such as the blood in which a bubble is growing, then the resistance is less than if the gas were transmitted to the interface purely by diffusion. The resistance imparted by such fluid boundary layers has been the subject of the most complex mathematical analyses all-too-characteristic of studies of fluid dynamics. For a comprehensive summary of convection and the more analytical approaches to solute transfer, the reader should consult the textbook by Rohsenow and Choi (1961).

On the other hand, engineers needing immediate practical solutions to heat and mass transfer problems have long adopted a semi-empirical approach by which they describe the resistance of each phase boundary by a film coefficient. This they relate to dimensionless groups of parameters, such as the Reynold's number, by empirical indices whose values are well established for the common flow situations. An elementary non-mathematical introduction to this technique applied to physiological problems has been presented by Hills (1974a).

Moving bubble

The study of bubble dynamics has been traced by Plesset (1963) to Besant and Rayleigh who formulated expressions describing collapsing bubbles containing vapour and insoluble gas. Starting from their simple equations, later writers have derived more general solutions to the expressions for bubble growth or collapse to account for heat transfer, mass transfer and force balance (Westwater, 1964).

Most interest in bubble dynamics has centred around boiling due to its great commercial importance in steam generation and petroleum refining but this is a particular case of vaporous cavitation where the surface tension is negligible and the limiting factor is heat transfer (Scriven, 1959). There are many treatments of bubble formation by gas transfer which account for viscosity (Szekely *et al.*, 1972), surface tension (Epstein and Plesset, 1950; Harvey, 1951a; Westwater, 1964; Nims, 1951; Hills, 1966; Albano, 1970; Albano and Columba, 1971) and, in static systems, the elasticity or compliance of the medium (Nims, 1951; Hills, 1966; Gent and Tomkins, 1969; Yang and Liang, 1972; Vann and Clark, 1975).

Most approaches approximate the boundary layer of the moving bubble to an encapsulating spherical shell of static fluid separating gas from the bulk of the fluid as though this were infinitely well stirred. Making further mathematical assumptions, Epstein and Plesset (1950) arrived at the solution that the rate of change of bubble radius (r_b) is given by

$$\frac{dr_b}{dt} = \frac{DS(\Delta p)}{\rho_g}\left[\frac{1}{r_b} + \frac{1}{\sqrt{(\pi Dt)}}\right] \quad (15)$$

where Δp is the degree of supersaturation of the bulk of the liquid phase relative to bubble gas (i.e. the driving force for growth), D is the diffusion coefficient, S is the solubility expressed as a volume of gas reduced to standard pressure per unit volume per unit tension, while ρ_g is the gas density expressed in the same volume units of gas per unit volume of the gaseous phase. Equation 15 was also obtained by Yang *et al.* (1972).

For large times (t) or small bubbles ($1/r_b$ large), the term $1/\sqrt{(\pi Dt)}$ in Equation 15 can be ignored relative to $1/r_b$ (Westwater, 1964), when the bubble radius can be derived as:

$$r_b = \sqrt{(2S(\Delta p)Dt/\rho_g)} \quad (16)$$

Similar expressions have been derived by Szekely *et al.* (1972), while Liebermann (1957) points out that increase in surface tension with an expanding surface area could cause Δr_b to fall below the predicted value for an expanding bubble.

Making the assumption that the effective diffusion shell has an equivalent thickness (d) equal to the bubble radius, Bateman and Lang (1945) use the following expression for the change in bubble volume (V_b):

$$dV_b/dt = RTASD(\Delta p)/Pd \qquad (17)$$

where R is the universal gas constant, T is the absolute temperature and A is the surface area. An equivalent form of this expression has been used by Harvey (1951a), Wyman *et al.* (1952) and Buckles (1968).

Experimental studies Wyman *et al.* observed the decay rate of bubbles in stirred unsaturated sea water to calculate that the diffusion shell had an effective thickness (d) of 33 μm. Bateman and Lang (1945) obtained a linear relationship between $V^{1/3}$ and time for decompression of water to 193 mm Hg while, at higher pressure (293 mm Hg), there was linearity between $V^{2/3}$ and t. This change can be explained by the fact that, by measuring the total volume of a gas solution, these authors were really monitoring a complex mixture of growth superimposed upon time-dependent nucleation (Hills, 1966). Because of this, results based upon direct observation of individual bubbles should be much simpler to interpret and more meaningful in establishing the nature of bubble growth.

Thus Liebermann (1957) observed small stationary bubbles and those allowed to rise freely in supersaturated water to find $r_b \propto t^{1/2}$. A greater time dependence ($r_b \propto t^{4/5}$) was found by Yang *et al.* (1972) for larger bubbles rising freely and more so ($r_b \propto t$) for 'stagnation' flow.

Multiple and reactive gases

When the bubble contains several gases, then the appropriate growth equation must be applied to each gas separately. They only interact in so far as Dalton's law must apply to the gaseous phase only, i.e. Equation 3 must hold. Thus, if one gas is being taken up very rapidly by a bubble because it is very soluble (e.g. nitrous oxide) or has a high diffusion coefficient (e.g. helium), the other gases will be diluted and their partial pressures in the bubble reduced accordingly. In this way, if a subject with a predominantly nitrogen bubble is switched to helium, not only will the bubble grow as a result of its faster uptake of helium but the dilution of bubble nitrogen by helium will reduce the rate of loss of nitrogen by counter-diffusion—as demonstrated experimentally in gelatin solutions by Strauss and Kunkle (1974).

When one of the bubble gases can react with the diffusion medium, such as oxygen with blood pigments, the rate of transfer is greater than predicted for an inert gas of the same solubility and diffusivity. In very broad terms, this arises because the solubility (S) is effectively replaced by the rate of change of content (C) with tension (p) at equilibrium, i.e. (dC/dp) is substituted for S where there is rapidly reversible assimilation of the gas. This type of analysis has been applied to the specific case of the uptake of oxygen from a bubble by blood (Tanasawa *et al.*, 1971; Hlastala and Fahri, 1973).

Reversible chemical affinity of the medium for the transmitted gas can also lead to facilitated diffusion (Wittenberg, 1970) such as oxygen by haemoglobin (Scholander, 1960) and carbon dioxide by buffers (Schoenfisch *et al.*, 1975).

Static bubble

The resistance to the transfer of any one gas across the air–liquid interface of a bubble is determined almost entirely by the boundary characteristics of the liquid. By comparison, other gases in the bubble make a negligible contribution to the overall resistance even though this may be slightly higher if they are being transmitted in the opposite direction (Hills, 1971c). The basic reason is that the mutual diffusion coefficient for one gas across another is of the order of 10^4 times larger than for the same gas across liquid water. However, this applies to resistance only and not to the effect on the driving force arising by dilution of the transmitted gas by other gases within the bubble as indicated in the previous section. Hence there is negligible error in assuming that the gases are effectively 'fully stirred' within any bubble of the size envisaged in decompression sickness.

The rate-controlling resistance for bubble growth is therefore determined by the liquid boundary layer and by the overall spatial

distribution of gas within extravascular tissue in the case of the static bubble. Thus it is easy to interpret the faster onset of symptoms with exercise (p. 45) as the more rapid growth of bubbles to symptom-provoking dimensions due to the introduction of some convective transfer into an otherwise static system; although there are alternative explanations (p. 96).

In the perfectly static situation, the rate of transfer ($\dot{g}$) of any one gas across the phase boundary, e.g. into the bubble, is given by applying Fick's law of diffusion to the interface, i.e.

$$\dot{g} = ASD(\partial p/\partial r)_{r=r_b} \qquad (18)$$

where $(\partial p/\partial r)$ is the tension gradient of that particular gas at the surface of the bubble ($r = r_b$). A word of caution in maintaining dimensional homogeneity when using Equation 18: if the Bunsen coefficient is used for the solubility (S), then $\dot{g}$ will have dimensions of partial molar volume of that gas (reduced to standard pressure) per unit time. In a multi-component bubble, this equation must be applied to each gas individually in order to obtain the net volume change of the bubble, $\dot{g}$ being negative for a dissolving gas.

A quick comparison of Equations 17 and 18 shows that the Bateman and Lang equation is really an approximation of the general expression (18) in which the gradient $(\partial p/\partial r)_{r=r_b}$ is approximated to a linear tension drop (Δp) across the equivalent unstirred shell of thickness (d), i.e. to ($\Delta p/d$). While this can be justified in flowing systems, no such approximations can be used in the case of a bubble growing in a static medium.

However, the gradient at the interface $(\partial p/\partial r)_{r=r_b}$ can only be estimated by first determining the overall tension distribution within the diffusion medium, i.e. p as a function of spatial location (r) and time (t). This is a particularly difficult task but one which has three logical steps.

(1) Setting up the general differential equation which applies at any point in the medium and which describes all of the physical and chemical processes involved.

(2) Determining the 'boundary conditions' to be applied to this comprehensive equation to describe the influence of conditions beyond the diffusion medium. These refer to both moving boundaries, such as the surface of a growing bubble, and to fixed boundaries determined by tissue geometry which would also apply before any bubble is formed.

(3) Attempting to obtain an analytical solution to the differential equation for those boundary conditions or, otherwise, using numerical techniques.

The comprehensive equation

Although Fick's law of diffusion might appear very simple when described in terms of steady-state conditions (fig. 64(a)), its form needed to describe transient situations is much more complex and reference is often made to it as the Fick-Fourier equation. However, even this can be further complicated in living tissue by any gas transfer effected by blood perfusion and metabolic assimilation or production of that gas. Each of these factors can then contribute a term to the Fick-Fourier equation describing the rate of change of gas tension $(\partial p/\partial t)$ at a general point of radial location r, i.e.

$$\partial p/\partial t = D.\nabla^2(p) + \lambda\dot{Q}(p_0 - p) - M_0 \qquad (19)$$

(transfer by diffusion) (transfer by blood perfusion) (consumed by metabolism)

where ∇^2 is the Laplace operator, λ is the blood: tissue partition coefficient for the gas, $\dot{Q}$ is the blood perfusion rate defined as the effective volume of blood equilibrating with tissue per unit volume of tissue per unit time, p and p_0 are the gas tensions of efferent and afferent blood and M_0 is the rate of tension fall or rise due to any metabolic consumption or production of the gas. Thus $M_0 = 0$ for an inert gas and it is positive for oxygen and negative for carbon dioxide. The diffusion term becomes zero if there are no gas gradients.

Numerous approximate solutions to this equation have been derived by Van Liew and co-workers which have offered good interpretations of their data for the resolution of tissue gas pockets which are very large relative to

intercapillary distances when, on such a macro-system, blood perfusion can be regarded as effectively uniform. These solutions are described in more detail later in connection with the perfusion: diffusion confusion (p. 167) and treatment.

While the universal nature of Equation 19 might have great appeal, it assumes uniform 'percolation' of tissue by blood. Thus it is of limited application to decompression sickness, since any extravascular bubbles are likely to be much smaller than the distance between the capillaries to which blood flow is restricted in practice, so that macro-scale mathematics can no longer be applied to such a localized situation.

In this case, account can be taken of blood perfusion, not by including it as a discrete term in Equation 19, but by recognizing that flow is confined to vessels whose walls then represent boundaries to the diffusion medium. These then impose boundary conditions related to the rate of flow and state of the perfusing blood.

Boundary conditions If their location is known, then these fixed-boundary conditions can be applied in the standard mathematical forms exactly analogous to those widely used to describe thermal conduction in solids (Carslaw and Jaeger, 1959) but it is often necessary to make extensive approximations to the geometric model envisaged in order to obtain an analytical solution. These fixed-boundary conditions also apply in determining the distribution of the particular gas as a function, $\theta(r;t)$, of distance (r) and time (t) *before* any nucleus is activated into growth, i.e.

$$\Delta p = \Delta p_b.\theta(r;t) \qquad (20)$$

where Δp is the change in tissue tension at that point at time (t) after a change (Δp_b) in blood tension of that gas.

Even though expressions for $\theta(r;t)$ may appear most cumbersome for even the simplest models, this is nothing by comparison with the mathematical complexity introduced by the moving boundary in the form of the gas–tissue interface of the growing bubble.

Some workers (e.g. Nims, 1951 and Bateman, 1951) seek mathematical simplicity by considering the case of gas diffusing into a vapour cavity, i.e. initially a near-vacuum of fixed dimensions. However, this is incompatible with the compliant nature of tissue and effectively ignores the fact that the bubble surface area (A in Equations 17 and 18) can change by several orders of magnitude during growth from a nucleus ($r = r_n$).

Although much less elegant mathematically, the computer can be used to 'number crunch' solutions to these moving boundary problems by applying finite difference techniques to concentric spherical tissue elements of constant volume whose inner and outer radii change as the bubble grows or shrinks. However, it has been the writer's experience that the programmer is then faced with the difficult problem of obtaining the correct degree of coarseness of the elements if he is to avoid the programme 'going critical'—especially when r_b may change by an order of magnitude or two.

Having outlined the basic requirements for calculating the rate of transfer of a gas from its solution into a stable gaseous phase, it is now appropriate to consider the feasibility of predicting the kinetics for the overall separation of gas from solution.

Overall separation of gas

The depressing theme emerging from this discussion is that the separation of gas from solution is determined by a closely interrelated combination of nucleation and growth. Unfortunately, the activation of nuclei is not well understood and even when quantitative description is possible, it often requires statistical treatment of a process which is somewhat random with respect to location and probably also to time. By comparison, growth can be very precisely described in differential form but the solutions involve immense mathematical complexity in view of the fixed and moving boundary problems, not to mention the alternating patency or 'flickering' of capillaries which would superimpose stochastic theory.

Hence it is only feasible to attempt to predict

and to quantify gas separation from solution if numerous assumptions are made.

Actual approaches

These modifications include not only approximations to the physical model but different assumptions regarding the role of the gaseous phase in inducing decompression sickness. This being so, the nature of the assumption(s) provides a convenient means of selecting the major approaches to the prevention of decompression sickness from the overall list of models and calculation methods as they are introduced in historical order in the next chapter.

(1) The original Haldane approach and its multitude of later modifications (p. 110) effectively avoid any calculation of the rate or degree of gas separation by working to a 'trigger point', presumably to nucleation. If this critical threshold is violated, then the subsequent growth of the gas phase is assumed to have no effect in determining the outcome of the dive. Hence their calculations never need to allow for a gaseous phase provided they never exceed these 'trigger points' and their descriptions of these nucleation thresholds is correct. It is further assumed that there are no tension gradients, so that no boundary conditions, either fixed or moving, need to be invoked.

(2) Workers at the Royal Naval Physiological Laboratory (p. 123), notably Hempleman and Rashbass, have similarly avoided growth by working to a 'trigger point' but have taken a linear diffusion model as the mode of uptake. By so doing they avoid moving (but not fixed) boundary conditions but have then averaged tissue gas tension over the whole slab before applying their critical conditions for nucleation—a practice also adopted by Wittenborn for a radial diffusion model (p. 123).

(3) U.S. Air Force workers (p. 126) during the Second World War, notably Nims and Bateman, paid much attention to the growth of a bubble to a critical gas content but for calculation purposes regarded the boundary of the bubble as fixed. They allowed for diffusion gradients but avoided any fixed boundary conditions imposed by the tissue by assuming the medium to be effectively infinite. The exchange of dissolved gas between blood and tissue was then assumed to be limited by blood perfusion by reverting, in effect, to Equation 18 for a non-metabolic gas ($M_0 = 0$) i.e. using a macro-approach although the fixed dimension taken for the bubble would suggest a micro-system.

(4) The 'Thermodynamic' approach effectively ignores growth by looking only at the 'worst possible case' of random nucleation, i.e. only at a region where activated nuclei are so dense that any gas in supersaturated solution is rapidly 'dumped' and then coalesces more slowly to provoke pain later. Hence the immence of bends is determined simply by the volume of gas which must separate from solution to establish a quasi-equilibrium between liquid and gaseous phases, thus avoiding 'trigger point' considerations. These conditions are applied *at each point* within a diffusion model, although recent modifications allow for some limitation to be imposed by blood flow (p. 245). However, because this approach avoids fewer of the factors contributing to mathematical complexity, it is by far the most difficult to handle in deriving diving tables.

There are many variations to these four fundamentally different approaches as shall be seen in Chapter 5. However, they introduce two other aspects of the basic physical properties of gases and their solutions beyond nucleation and growth, viz. coalescence and the volume of gas which can be deposited from solution.

Coalescence

In an earlier chapter the evidence suggested quite strongly that the separation of gas from solution is not only the primary event but the degree of separation determines the critical insult for provoking most forms of decompression sickness. Since the activation of nuclei is

rapid, when it occurs, it raises the question of the reason for the delay in the onset of symptoms. Most proponents of theories of decompression sickness chose not to offer any explanation but Nims (p. 126) and Bateman (p. 126) attribute the induction period to growth of the bubble to pain-provoking dimensions. This feeling is also reflected by later workers (Griffiths *et al.*, 1971).

However, the delay in the onset of limb bends has also been attributed to coalescence of the gas initially 'dumped' from solution (Hills, 1966). The concept was introduced in order to explain the random distribution in the induction periods for bends to occur following the same decompression by the same individual (p. 33). Before attempting to compare the relative merits of this hypothesis with that based upon growth, however, it is desirable to know more about the physical nature of coalescence.

Thermodynamic considerations

Ignoring gravitational considerations, any phase suspended in another will reach its lowest overall energy when its total surface area is a minimum. Thus the lowest energy state for a gaseous phase dispersed in tissue or blood must occur when it has formed one bubble, the net energy change representing a driving force favouring coalescence; although Liebermann (1957) emphasizes the stability of bubbles lying in juxtaposition.

Two bubbles can merge into one either by direct fracture of the thin liquid film separating them or by one growing at the expense of the other as gas diffuses across the intervening fluid film (Hills, 1966). Since it is most unlikely that two bubbles meeting in tissue would be of equal size, the smaller would have a higher internal gas pressure by virtue of surface tension. The differential internal pressure between the two bubbles would provide the driving force for the diffusion of gas from the smaller to the larger. Hempleman (1969) has pointed out that this can explain the observation that, on the average, 'bends' tend to occur sooner after heliox dives than air dives, helium taking less time to diffuse from one bubble to the other by virtue of its appreciably higher diffusion coefficient. However, differential diffusion rates can also be invoked to provide an equally plausible explanation for the difference in *average* induction periods on a purely growth-limiting hypothesis. It is therefore desirable to look at the kinetics of coalescence in more detail before attempting to compare these theoretical approaches more critically.

Kinetics of coalescence

The first requirement for two bubbles to merge into one is that they come in contact, at least to the extent that they cause mutual deformation of each other. There would therefore seem to be two aspects to the kinetics of coalescence, both of which are best interpreted by probabilistic considerations. These are:

(a) the probability of any two bubbles or other masses of gas meeting. This would apply to a merger either by bursting the intervening film or by gas diffusion across it; and

(b) the probability of bursting this membrane must depend upon the number of collisions and extent of mutual deformation.

The probabilistic nature of both of these events is particularly compatible with the random distribution of the onset times of symptoms (p. 33).

Coalescence versus growth

Both steps in the coalescence of two bubbles should be greatly accelerated by motion. Simple experiments with two bubbles trapped at an oil–water interface, or with two globules of mercury on a clean glass plate, show that the number of collisions is a most significant parameter in determining the likelihood of coalescence (Hills, 1966). There would appear to be an equal probability of two bubbles merging at any collision after the first.

This is interesting because the alternate contraction and elongation of a muscle would seem to provide a motion most conducive to

the coalescence of gas initially deposited as films or micro-bubbles within the locomotor system and its adjacent connective tissues. Hence it is most significant that exercise during or after decompression can greatly accelerate the onset of symptoms (p. 45).

It is difficult to explain this fact on the basis that growth of the bubble delays the 'bends', since the increased vasodilation and blood perfusion associated with exercise would enable blood to compete more successfully with the bubble in draining the supersaturated regions of tissue (see fig. 27). This would not only tend to divert gas away from the bubble and reduce its growth rate but would also reduce its ultimate size and hence its likelihood of provoking symptoms. However, the 'bends' incidence is *increased* with exercise—at least, with a U.S. Navy style of decompression. The long first 'pull' towards the surface so characteristic of their profiles (fig. 51) is likely to deposit much sub-symptomatic gas from solution. This gas is then most prone to coalesce in an exercising subject and so provoke bends before much of that gas can be removed from the system. Accordingly the effects of exercise would appear to be easier to explain by coalescence delaying the onset of decompression sickness than by growth. On the other hand, one must not lose sight of the fact that exercise could also potentiate the 'bends', and their onset, through some haematological or biochemical factor contributing to the critical insult of the type described earlier (p. 55).

Another fact compatible with coalescence is the greater difficulty of resolving the clinical symptoms in a diver or caisson worker who has waited before seeking treatment. It is easy to envisage how gas deposited from solution would take longer to be resolved by recompression if left to coalesce or otherwise congregate into a large bubble.

Coalescence would also seem to offer a rather more plausible explanation than growth for the occasional case where bends can actually be induced, or the pain increased, by recompression—an act which could cause bubbles to 'pop' together. In this way they could produce a greater deformation of a local nerve ending despite their individual reduction in volume.

Intravascular bubbles

So far we have only considered the coalescence of extravascular gas. However, since circulating gas emboli are likely to be responsible for some forms of decompression sickness, particularly those Type II manifestations involving higher centres of the brain (p. 63), it is also desirable

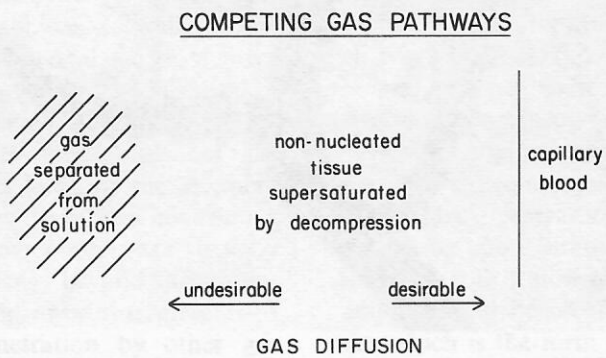

Fig. 27 Depicting the general philosophy of optimizing decompression: to change environmental parameters in such a way that dissolved gas supersaturated by decompression is transferred away from the tissue rather than 'dumped' into the nearest bubble or 'activated nucleus'

to look at bubble behaviour *within* blood vessels.

Studies of bubble coalescence within a fluid have been conducted in the physical sciences but usually the work has involved static or stirred liquids in large containers. However, it is well established that bubbles are more likely to co-exist in juxtaposition if the surface tension is reduced by a surfactant of which there are many present in the body—particularly in the lungs (Pattle, 1966). Many components of blood display various degrees of surface activity. Thus Harvey *et al.* (1944a, b) predicted that intravascular coalescence would not occur since protein and lipid materials in the blood form a monolayer on the bubble surface.

Coalescence of gas in actual blood vessels has been mentioned as an aside in several studies of the behaviour of an injected bolus of air observed in the body—such as through a cranial window (De la Torre, 1962; Waite *et al.*, 1967). While this work confirmed that

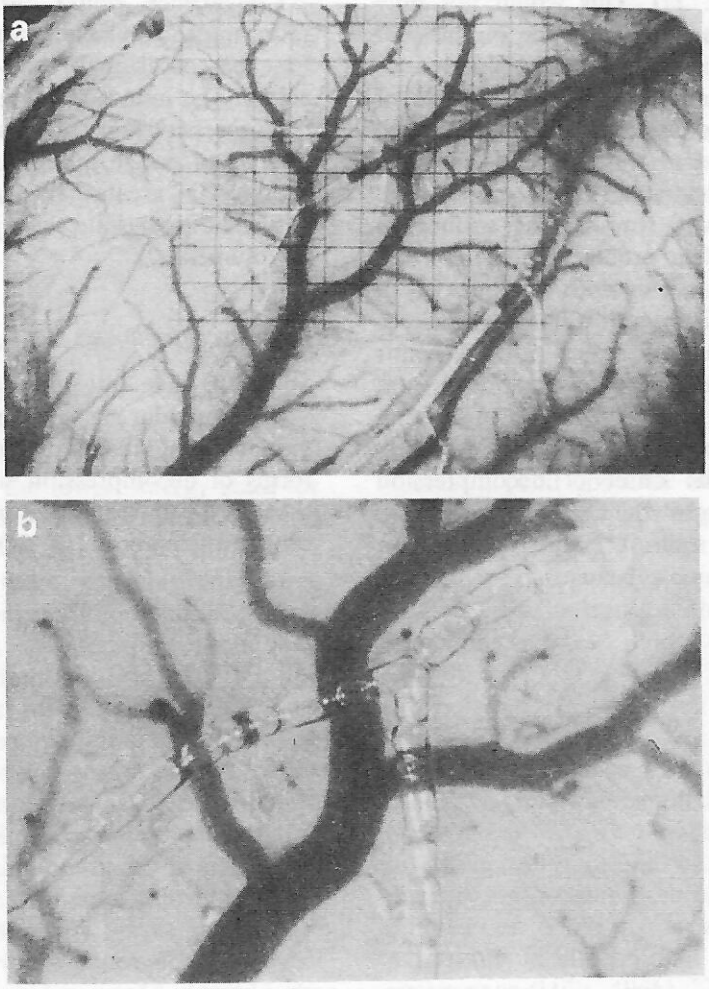

Fig. 28 Showing a large number of injected microbubbles (80 μm diameter) (a) accumulating within a small artery in the cerebral circulation of a guinea pig and (b) some time after, when they form slugs of gas whose length is about 1½ times the vessel diameter--a very characteristic intermediate stage in coalescence. Described by Grulke and Hills (1976)

intravascular coalescence did occur, the observations were essentially confined to the merger of bubbles of widely varying size characteristically produced by random 'fracture' of the bolus and its fragments at vessel bifurcations (Curtillet, 1939).

Only recently have studies been made using known numbers of intravascular microbubbles of uniform and carefully measured diameters (Grulke and Hills, 1976; Grulke, 1975). This work shows that the nature of coalescence is greatly dependent upon number and size of the bubbles. A single microbubble of air in the arterial system (40–250 μm diameter) will travel with the velocity of blood until it reaches a vessel of smaller diameter, when it will deform and proceed more slowly. It then causes a dilatation of the distal arterial system to the extent that the path immediately ahead may be wider than that already transcended. However, it is soon deformed again as it passes to smaller dilated arteries and squeezes through maybe two to three smaller branches until it eventually stops at a vessel bifurcation to occlude flow.

If a second bubble enters the same artery prior to occlusion, then the first is retarded and will tend to lodge at an earlier bifurcation. Blood between the bubbles tends to 'filter' out through radiating arterioles until the second bubble catches up with the first. Subsequent bubbles behave similarly until they form a chain. When these bubbles, with cylindrical midsections imposed by the vessel walls, come close enough for their spherical ends to deform each other, coalescence can occur. This takes place in two stages—the coalescence of groups or pairs of bubbles to form 'slugs' of gas followed, often minutes later, by the 'popping together' of these 'slugs' to form a continuous column of air. These air columns are virtually static, never progressing beyond arterioles, i.e. the same level in the arterial tree recorded as the maximum penetration by other gas formations (Chase, 1934; Lever *et al.*, 1966; Buckles, 1968). Long intravascular gas columns have been found post-mortem both clinically and experimentally following cerebral air embolism (Chase, 1934; Fries *et al.*, 1957).

When a large number of microbubbles enter an artery they almost invariably coalesce within 5–30 seconds of forming intimate accumulations. Once again, they form these characteristic 'slugs' whose lengths are typically 1·5–2 times the vessel diameter. They then 'pop together' at some later time and often do so simultaneously as though a pressure wave were passing down the vessel. A typical sequence of events for air microbubbles is shown in fig. 28.

However, microbubble accumulations are much less conducive to coalescence in the arterial system if they contain oxygen or the subject is ventilated on pure oxygen (Grulke and Hills, 1976)—an interesting aspect discussed in connection with treatment (p. 230).

Other aspects of coalescence

Another aspect of coalescence which appears to have received little attention is the ability for one bubble passing over a surface to 'wipe off' and engulf any other bubbles in its path which were attached to the surface. A simple analogy is afforded by the water droplet running down a 'steamed up' window pane on a cold day. This could provide a simple mechanism whereby microbubbles released by decompression could be coalesced within vessels much larger than any they could occlude. This could occur at the top of large horizontal vessels and could well account for some of the strange effects of body orientation on gas exchange and the incidence of decompression sickness, Balldin (1976) providing experimental evidence on xenon clearance to emphasize the importance of posture.

A similar phenomenon may be responsible for the 'irregular gas masses' which Harvey (1951b) has observed by microscope in connective tissue upon withdrawing the round end of a glass rod following decompression. This action would be ideal for coalescing films of gas which is the form in which this writer has found gas deposited at an oil–gelatin interface (Hills, 1966)—a form in which *intracellular* gas would be very difficult to observe unless coalesced. This differs from the popular explanation which postulates that lifting the rod

away from the tissue causes a local negative pressure which augments atmospheric decompression (Harvey, 1951b; Vann and Clark, 1975). However, it can be argued that removing the rod reduces the local pressure in the region of indentation, but this still remains positive relative to adjacent tissue areas. Hence gas separation in tissue may be much more extensive than generally believed but it needs to be partially coalesced before it can be observed. This, perhaps, offers a warning against always thinking of separated gas in terms of bubbles—just one shape which it can assume.

Collision fission

Another novel phenomenon is collision fission of microbubbles (Hills, 1974b) which would appear to be the reverse of coalescence. Microbubbles of diameter less than 200–250 μm formed by the injection of air into human plasma *in vitro* burst into many smaller bubbles on collision. Their size has little effect on those of the progeny (40–50 μm). On the other hand, larger bubbles (> 500 μm) tend to coalesce in the same media. It is tempting to speculate that collision fission is a possible protective mechanism by which the body might minimize the pathological effects of air emboli by reducing their size, although increasing their number.

At first sight collision fission may appear to be incompatible with the thermodynamic argument previously advanced for the driving force for extravascular coalescence under essentially *static* conditions. However, the phenomenon has only been observed under *dynamic* conditions where dispersion of a large bubble into smaller ones reduces the net terminal velocity of the gas and hence the kinetic energy associated with its rise under gravitational forces.

One of the interesting findings is that the ultra-microbubbles produced by collision tend to dissolve, supersaturating the plasma with respect to ambient pressure! This can be attributed to the rise in internal pressure of bubbles imparted by surface tension ($2\gamma/r_b$) as the radius (r_b) is reduced.

However, if nothing more, the phenomenon shows how the mechanical state of the gas can influence the position of phase equilibrium (fig. 29).

Phase Equilibrium

The activation or formation of nuclei and their subsequent growth into bubbles are essentially kinetic processes. Even though the mechanism of nucleation may not be known, nor the immensely complicated mathematics associated with growth solved, there is little difficulty in describing the equilibrium position which both nucleation and growth are striving to attain. *In vivo*, at least, this asymptotic state should strictly be termed a quasi-equilibrium, since it represents an idealized situation which would be achieved by decompression *before* the overall gas content of the tissue was altered significantly by gas exchange with circulating blood.

However, before determining this maximum volume of gas which could be precipitated by a pressure change, it is necessary to express the conditions for phase equilibrium in terms conducive to decompression analysis.

The gaseous phase

The total hydrostatic pressure within any bubble must exceed ambient, the excess (B) being contributed by tissue compliance (δ_g) and surface tension ($2\gamma/r_b$) in accordance with Equation 14. Moreover, by Dalton's law, the total pressure of gas in the bubble ($P+B$) must equal the sum of the partial pressures as depicted in fig. 26.

If this argument is extrapolated to an inactive nucleus, mechanical equilibrium is given by

$$\Sigma p' = P + B' = P + \delta_g + 2\gamma/r_n \qquad (21)$$

so, that B' now represents the minimum degree of supersaturation needed to activate that nucleus into growth, defining supersaturation relative to ambient pressure (P). Thus the 'reservoir of nuclei' probably present have a spectrum of B' values corresponding to their range of radii (r_n).

Liquid phase

Activation of the nucleus into growth will

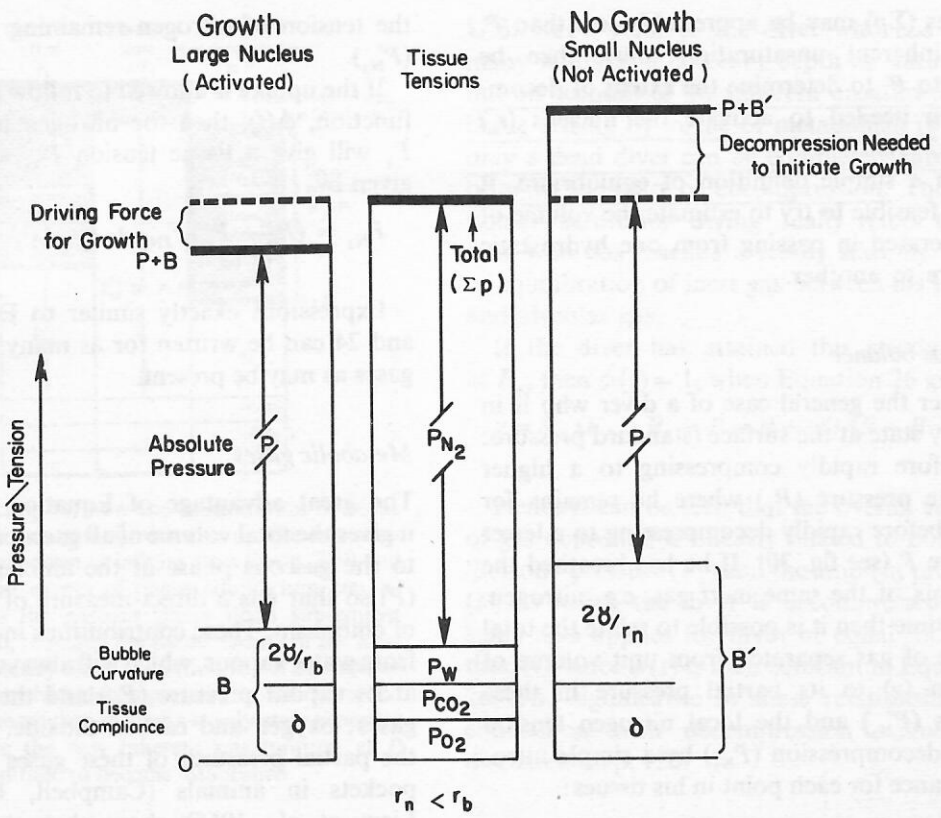

Fig. 29 Depicting how a nucleus (radius r_n) will not grow if the sum of the local tensions of the various tissue gases does not exceed the hydrostatic pressure within, while it *will* grow and become a bubble (radius r_b) if the reverse holds (Equation 22)

depend upon whether the sum of the tensions of dissolved gases exceeds $(P + B')$ and the condition for bubble growth can now be rewritten to read that activation of a nucleus will occur if

$$\Sigma p > P + B' \qquad (22)$$

where Σp is now the total tension of gases *in solution* rather than in the gaseous phase ($\Sigma p'$). Thus B' represents a critical degree of supersaturation (relative to ambient pressure) needed for the dissolved gases to activate that nucleus into growth. The significance of B' is depicted in fig. 29 which shows both the condition for nucleus activation (Equation 22) and the driving force for growth of a bubble after inception. This leads to the following important questions.

(1) Is B' a significant value in tissue?

(2) Is B' a constant or is it a function of environmental conditions—particularly absolute pressure?

(3) In avoiding decompression sickness, should the average value of B' be used for the whole spectrum or the lowest value representing the worst possible case?

These questions form the basis of the most important of the vital issues on which decompression theories differ (see Chapter 6). While the answers can only be obtained by considering actual diving data, at least the foregoing discussion of the physics of bubble formation enables the problem to be formulated simply.

In using the simple expression above (Equation 22), it must be remembered (Chapter 1) that Dalton's law does not apply in the liquid phase, i.e. $\Sigma p \neq P + B$ and that the sum of the

tensions (Σp) may be appreciably less than P. This 'inherent unsaturation' must then be added to B' to determine the extent of decompression needed to activate the nucleus (r_n) (see p. 243).

With a simple definition of equilibrium, it is now feasible to try to estimate the volume of gas liberated in passing from one hydrostatic pressure to another.

Inert gas balance

Consider the general case of a diver who is in a steady state at the surface (standard pressure: P_0) before rapidly compressing to a higher absolute pressure (P_1) where he remains for time τ before rapidly decompressing to a lesser pressure P (see fig. 30). If he has breathed the same mix of the same inert gas, e.g. nitrogen, all the time then it is possible to relate the total volume of gas separated from unit volume of solution (v) to its partial pressure in these bubbles (P'_{N_2}) and the local nitrogen tension before decompression (P_{N_2}) by a simple nitrogen balance for each point in his tissues:

$$vP'_{N_2} = S_{N_2}.P_{N_2} - G_e - S_{N_2}P'_{N_2} \qquad (23)$$

(N_2 separated from solution) (in solution before decompression) (eliminated) (left in solution)

where S_{N_2} is the solubility of nitrogen and G_e is the N_2 eliminated during decompression. This expression (Hills, 1966, 1969c) assumes that growth goes to completion, so that the nitrogen partial pressure in separated gas has reached the tension of nitrogen remaining in solution (P'_{N_2}).

If the uptake is allowed to follow any general function, $\phi(t)$, then the nitrogen taken up at P_1 will give a tissue tension P_{N_2} after time τ given by

$$P_{N_2} = \underset{(N_2 \text{ before compression})}{(P_0 - P_w)F_{IN_2}} + \underset{(N_2 \text{ taken up})}{F_{IN_2}(P_1 - P_0)\phi(\tau)} \qquad (24)$$

Expressions exactly similar to Equation 23 and 24 can be written for as many other inert gases as may be present.

Metabolic gases

The great advantage of Equation 23 is that it gives the total volume of all gases contributing to the gaseous phase at the ambient pressure (P) so that v is a direct measure of the degree of embolism. These contributions include those from water vapour, which will always be present at its vapour pressure (P_w) and the metabolic gases: oxygen and carbon dioxide. Studies of the partial pressures of these gases within gas pockets in animals (Campbell, 1924; Van Liew *et al.*, 1965) show that their partial pressures very rapidly revert to near-venous values following any change in external pressure. Since gas separated from solution by decompression would be more finely dispersed and in more intimate contact with tissue, there is little approximation in assigning venous values to these gases. Substitution of venous values in Equation 14 then gives the partial pressure of separated gas (P'_{N_2}) as

$$P'_{N_2} = P + B - \underbrace{P_{vO_2} - P_{vCO_2} - P_w}_{m} = P + B - m \qquad (25)$$

That is, the nitrogen essentially takes up the difference between the total gas pressure ($P + B$) and the sum of water and metabolic gas tensions (m) as needed to effect a mechanical balance of the type shown in fig. 26. /p. 86

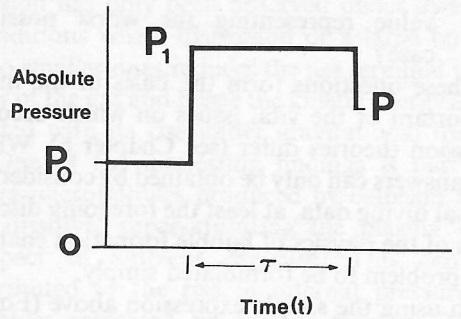

Fig. 30 Depicting a simple exposure to an absolute pressure P_1 for time τ, followed by rapid decompression to a general absolute Pressure P

Volume of 'dumped' gas

The maximum volume of gas will be deposited from solution when decompression is rapid and growth of the gaseous phase is virtually complete before any significant amount of

(25) ≡ $P'_{N2} = P_{amb} + P_{bubb} - m$

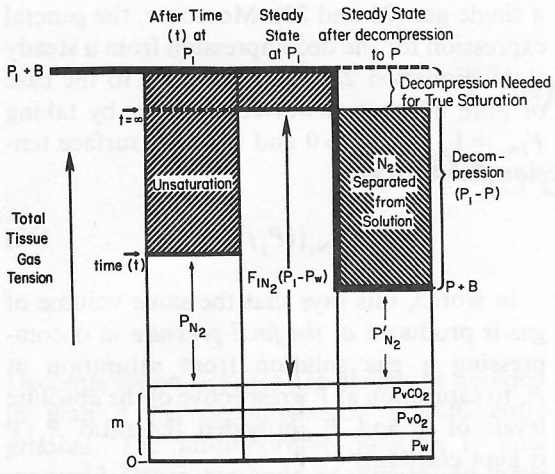

Fig. 31 Depicting (a) how the unsaturation of tissue decreases with continuing nitrogen uptake but does not become zero even at infinite time (see p. 239) and (b) how gas in excess of phase equilibrium can be 'dumped' into the gaseous phase upon subsequent decompression, reducing the tissue tension of the inert gas rather than any other (Equation 25). It also shows how much immediate decompression would be needed to produce true saturation after a steady-state exposure ($t \simeq \infty$) before the new inherent unsaturation at P had time to become established

nitrogen is eliminated, i.e. $G_e = 0$. Making this substitution and eliminating P'_{N_2}, P_{vO_2}, P_{vCO_2} and P_w from Equations 23–26 gives the total volume of all separated gas at ambient pressure (P) as

$$v = S_{N_2}\{[P_0 + (P_1 - P_0)\phi(\tau)]F_{IN_2} - P - B + m'\}/(P + B - m) \quad (26)$$

where

$$m' = m - P_w . F_{IN_2} \quad (27)$$

Equation 26 describes what is essentially the maximum volume of gas which can separate from solution for a limited duration (τ) on the bottom (at P_1). As expected, it can be seen that this is particularly dependent upon the solubility of the inert gas. The volume will be greatest when the diver has remained at depth for an effectively infinite time and so reached a steady state.

Decompression from a steady state

Many workers in the field, particularly the U.S. Navy, refer to the diver who has spent many hours at a constant depth as 'saturated' but on account of the inherent unsaturation in tissue arising by virtue of metabolism (p. 239) only a dead diver can be completely saturated prior to the start of decompression. The misnomer 'saturation diving' really refers to the man who has reached a steady state by virtue of equilibration of inert gas between his tissues and alveolar gas.

If the diver has attained this steady state at P_1, then $\phi(\tau) = 1$, when Equation 26 gives

$$v = S_{N_2}(F_{IN_2} . P_1 - P - B + m')/(P + B - m) \quad (28)$$

Hence it can be seen that the overall volume of gas deposited is linearly related to both the 'bottom' pressure (P_1) and the ambient pressure (P) to which the diver is decompressed. The same also applies for dives of equal 'bottom' time (τ), since $\phi(\tau)$ is then constant in Equation 26. The significance of these relationships in connection with decompression sickness is discussed on p. 120.

Multiple inert gases

For the purpose of outlining the principle involved in determining the degree of embolism (v), it was convenient to consider just one inert gas and a popular one at that, viz. nitrogen. However, equations exactly similar to 23–28 can be derived for helium or any other inert gas using the appropriate constants. It is now quite common practice in diving to breath several inert gases simultaneously or to switch from one to another. For this reason it is highly desirable to know the new volume, its contributions from each inert gas and hence the individual driving forces for eliminating or taking up each inert gas.

A helium balance can be written in a form exactly similar to Equation 23 which, for negligible elimination ($G_e = 0$), can be re-arranged to give

$$P'_{He} = P_{He} . S_{He}/(v + S_{He}) \quad (29)$$

The mechanical gas balance (Equation 25) must be revised to include helium and any other inert gas (i) as

$$P'_{N_2} + P'_{He} + P'_i = P + B - m \quad (30)$$

where P'_{He} and P'_i are the partial pressures of helium and any other inert gas (i) in the gas separated from solution. These values are not known but can be eliminated using Equations 23 (for $G_e = 0$) and 29 to give an expression for the overall gas volume (v):

$$P + B - m = \frac{P_{N_2} \cdot S_{N_2}}{(v + S_{N_2})} + \frac{P_{He} \cdot S_{He}}{(v + S_{He})} + \frac{P_i \cdot S_i}{(v + S_i)} \quad (31)$$

where P_{He} and P_i are the tissue tensions of helium and any other inert gas (i) *before* decompression.

There are now enough equations to solve for the unknowns: P'_{N_2}, P'_{He}, P'_i and v, this reducing to a quadratic for just two inert gases, so that, by using actual values for P_{N_2}, P_{He}, B and m, it is possible to determine both the total volume of separated gas and the contribution from each inert gas. By Avogadro's law, these contributions must be proportional to their respective partial pressures in the gaseous phase (P'_{N_2}, P'_{He}, etc.) when it is interesting to see from Equations 23 and 29 that nitrogen and helium contribute neither in proportion to their pre-decompression tissue tensions (P_{N_2} and P_{He}) nor to the corresponding concentrations ($P_{N_2} . S_{N_2}$ and $P_{He} . S_{He}$) but to something in between.

Single gas in vitro

It can be seen that for the case where nitrogen is the only inert gas present, the multiple inert gas equations (30 and 31) revert to those for a single gas (25 and 23). Moreover, the general expression for the decompression from a steady state (Equation 28) can be applied to the case of pure nitrogen dissolved in water by taking $F_{IN_2} = 1$, $m = m' = 0$ and ignoring surface tension $B = 0$, to give

$$v = S_{N_2}[(P_1/P) - 1] \quad (32)$$

In words, this says that the same volume of gas is produced *at the final pressure* in decompressing a gas solution from saturation at P_1 to saturation at P irrespective of the absolute levels of P and P_1 provided the ratio P_1/P is kept constant.

This has been derived for this simple case by Piccard (1941); while the inference that the same volume of gas is liberated for the same decompression ratio (P_1/P) is also contained in the original publication of the 'Haldane' calculation method for preventing decompression sickness (Boycott *et al.*, 1908). However, it is important to appreciate the multiplicity of assumptions necessary in order to extricate a simple decompression ratio (P_1/P) from the much more complex relationship between P and P_1 likely to hold *in vivo* (Equation 28). Moreover, there is the particularly interesting implication that a near-constant volume of gas separating from solution is the only condition needed to produce a constant decompression ratio and hence to provide an alternative to limited supersaturation as the explanation for this popular ratio concept (p. 110) widely used in calculating tables for the prevention of decompression sickness.