Chapter 7

Other Vital Issues

Having discussed the critical conditions relating tissue gas content to absolute pressure for initiating the primary event and for the critical level of insult needed to provoke symptoms, the next problem in synthesizing a preventive method from fundamentals concerns how to estimate that gas content in the first place. This raises the question of the time course for the exchange of gases between the critical tissue(s) and the breathing mix, i.e. the kinetics of inert gas uptake and elimination *before* any asymmetry is introduced by undue decompression. This, in turn, raises the next vital issue concerning the perfusion : diffusion confusion.

Diffusion versus Blood Perfusion

To appreciate the nature of this vital issue, first consider a subject who has just switched his breathing mix from oxygen to air without any decompression. In fig. 55 it can be seen how the lungs permit 95–99% equilibration of arterial blood with nitrogen within 1–3 min of the switch, i.e. several orders of magnitude faster than the response time of the critical tissue(s) as indicated by kinetic aspects of decompression sickness (see fig. 12). Hence respiration can be ignored as a factor limiting gas uptake for all except very short exposures. It is therefore necessary to look closely at the transport processes within the tissue itself to determine what controls its assimilation of inert gas.

Tissue transfer processes

When blood enters the capillary bed of a peripheral tissue, the dissolved nitrogen will be diluted by the incumbent blood and because of the blood : tissue gradient which this reduced concentration affords, some will diffuse across the endothelial wall into the interstitial space.

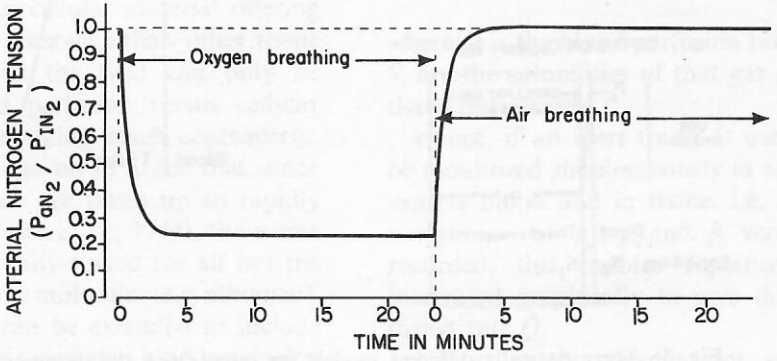

Fig. 55 Depicting the fall in arterial nitrogen tension (P_{aN_2}) on oxygen breathing and its increase upon return to air breathing. This demonstrates the time scale for the delay to the uptake of inert gases by the body imposed by the lungs. Redrawn from Ferris and Engel (1951)

The rest will return to the lungs *via* the veins which can be considered an overflow for this 'pool' of capillary blood. The nitrogen entering the interstitium (comprising some 10–60% of tissue volume) will increase P_{N_2} in that compartment which, in turn, provides a gradient for diffusion across the cell membrane and then into cytoplasm which is effectively static; although small currents have been observed in some cells (Taylor, 1965) and may introduce some convection. Thus the macro-distribution of inert gas is provided by the circulation while the micro-distribution is effected by its subsequent diffusion into extravascular tissue from the nearest blood, i.e. two transport processes in series. This qualitative description may sound very simple but the real problem in quantifying the system arises in determining which of these simple processes actually *limits* uptake or, if more than one, then what are their relative contributions in controlling blood: tissue gas exchange?

The controversy

Some designers of preventive decompression tables find it difficult to appreciate how a controversy can arise, or why such an issue is made out of perfusion versus diffusion; so a simple example may help. If only a few drops of blood were supplied to a whole limb each minute, then this very low blood flow and consequent very poor perfusion of the tissues, must limit transfer, since uptake cannot exceed the total delivery of that gas by blood. On the other hand, if there is an enormous flow of blood through each capillary, such that each molecule of inert gas is replaced as soon as one diffuses out into the surrounding tissue, then the rate of assimilation of that gas by the tissue as a whole must be limited by diffusion. Unfortunately, the normal physiological state of most tissues makes neither of these extremes an obvious choice and, since they can lead to different time courses for gas uptake, it

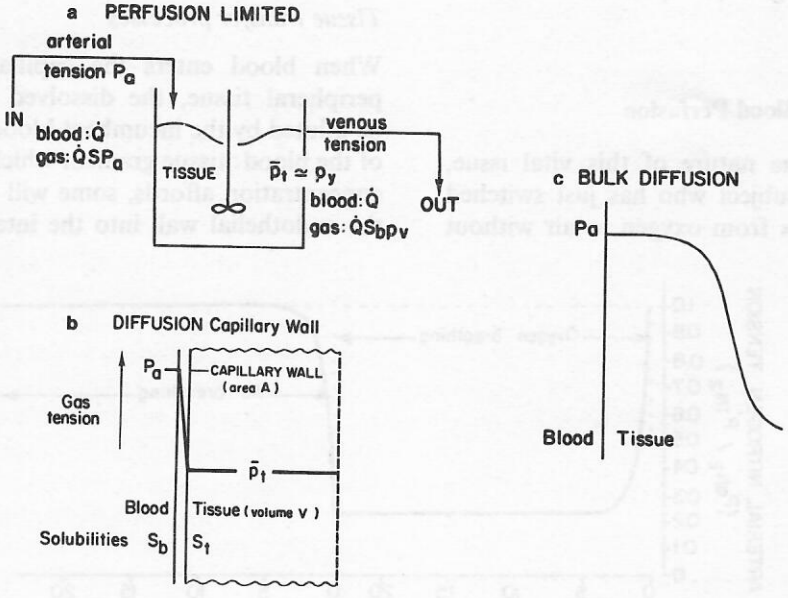

Fig. 56 Three basically different models for quantifying the uptake of dissolved gases by tissue in which the rate is limited by (a) the blood perfusion rate of the tissue, (b) diffusion across a membrane and (c) diffusion into the bulk of the tissue as a medium of homogeneous permeability

therefore becomes necessary to determine which of them is rate-limiting.

To be quite correct, the choice is not restricted to these two cases but to any of the transport processes mentioned in the qualitative example of nitrogen uptake described earlier and which can be itemized as the overall rate of delivery of gas to the tissue in the perfusing blood; diffusion across the capillary wall; diffusion from the interstitium across the cell membrane into cytoplasm; and diffusion into the bulk of the cytoplasm which represents the greatest potential reservoir for dissolved gas.

These and other 'serial barriers' to blood-tissue transport have been described in great detail in numerous papers collected by Crone and Lassen (1970). However, it is difficult to envisage the capillary wall offering any significant resistance to gas transfer since it is non-selective to molecules much larger than those of gases. In any case, the outward filtration of water at the afferent end of the capillary and its return at the efferent end should effect gas transport by hydrodynamic flow—which also extends into the interstitium. Moreover, the relatively high diffusion coefficients for gases in pericapillary filtrate, as reflected by lymph (the fluid drained from this compartment), leaves little doubt that the capillary 'pool' effectively includes the interstitial space.

On the other hand, the cell membrane is much more selective in its transport of physiologically active substances while cytoplasm has a consistency less fluid than lymph, so it is easier to envisage cellular material offering a greater diffusion resistance than other tissue compartments. Thus the field can only be narrowed to blood perfusion versus cellular diffusion without invoking much controversy. Many physiologists go on to argue that, since cations such as Na^+ are taken up so rapidly by tissue (e.g. Gellhorn *et al.*, 1944), the whole tissue is effectively fully-stirred for all but the solutes with very large molecules (e.g. albumen), so that the 'pool' can be extended to include the whole tissue. This view that blood perfusion is the sole rate-limiting process has been widely accepted in the physiological literature, a fact which should not be dismissed without reason by those advocating bulk diffusion models for decompression optimization (pp. 122–126) or when using tissue half-times for nitrogen and helium related by Graham's law of diffusion (p. 118). It is therefore necessary to see why blood perfusion was accepted as rate-controlling in the first place.

The literature

The perfusion:diffusion controversy is one of much wider physiological and clinical interest since it concerns: the rate of supply of nutrients to tissue; the rate of uptake of anaesthetic agents; and the estimation of local blood perfusion rates, in addition to predictions of the imminence of decompression sickness.

This leads to a very wide literature far too large to include in this chapter. However, before discussing the salient features selected for their relevance to this issue, certain fundamentals should be considered which apply irrespective of which process is rate-limiting.

Gas balance in tissue

Whatever process controls blood:tissue exchange, the mean tissue tension ($\bar{p}_t$) can be related to arterial (p_a) and venous (p_v) values at any time by a simple mass balance for the inert gas. This gives

$$\underset{\text{uptake from arterial blood}}{\dot{Q}S_b p_a} - \underset{\text{removal in venous blood}}{\dot{Q}S_b p_v} = \underset{\text{net accumulation}}{S_t(\mathrm{d}\bar{p}_t/\mathrm{d}t)} \qquad (58)$$

where $\dot{Q}$ is the blood perfusion rate and S_b and S_t are the solubilities of that gas in blood and tissue respectively.

Hence, if an inert tracer is used which can be monitored simultaneously in arterial blood, venous blood and in tissue, i.e. simultaneous variations in p_a, p_v and $\bar{p}_t$ versus t can be recorded, this enables Equation 58 to be integrated graphically to give the blood perfusion rate $\dot{Q}$.

Unfortunately, this is not so simple in practice. Whereas the tissue input can be controlled experimentally, e.g. a sudden switch to a fixed alveolar partial pressure P_a, giving

a step change 0 to P_a in p_a, it is usually much more difficult to monitor both p_v and $\bar{p}_t$. However, if blood perfusion is the rate-limiting process, then there would be no diffusion gradients, so that the tissue would effectively be one fully-stirred 'pool' (fig. 56(a)) whose tension must then equal that of the overflow. Hence, in the circulation-limited system, $\bar{p}_t$ can be equated to p_v, when Equation 58 can now be reduced to a very simple form which can be integrated for a step change (0 to P_a in p_a) to give

$$P_a - \bar{p}_t = P_a \cdot e^{-\lambda \dot{Q} t} = P_a \cdot e^{-kt} \qquad (59)$$

where λ is the blood : tissue partition coefficient (S_b/S_t).

Accordingly, a plot of $\log_e[(P_a - \bar{p}_t)/P_a]$ versus t should give a straight line of gradient $-\lambda\dot{Q}$, thus providing a particularly simple means of deriving the blood perfusion rate $(\dot{Q})$. This approach has therefore been very widely used in numerous physiological studies and as a routine clinical method for determining $\dot{Q}$. $\dot{Q}$ is a very useful clinical parameter since it represents the blood actually exchanging solutes with tissue, i.e. the *functional* blood flow and therefore is more meaningful than the overall circulation rate which would be recorded simply by monitoring flow in an artery leading to the tissue. Hence a great deal of physiological deduction would need revision if perfusion were not the sole rate-limiting process and Equation 59 were proved invalid. This also applies to the use of the exponential as derived in Equation 59 as the time function for 'Haldane tissues'.

This method, however, has not gained such wide acceptance without much evidence to support that view—particularly the work reviewed by Kety (1951), Roughton (1952) and Jones (1951)—and a very careful assessment of the key experiments is imperative before expressing any opinion to the contrary.

Does venous tension equal mean tissue tension?

Since diffusion and blood perfusion are mass transfer resistances in series, a very direct means of deciding which predominates should be afforded by measuring the tension at the junction between them, i.e. in the capillary wall. The latter represents an impossible task

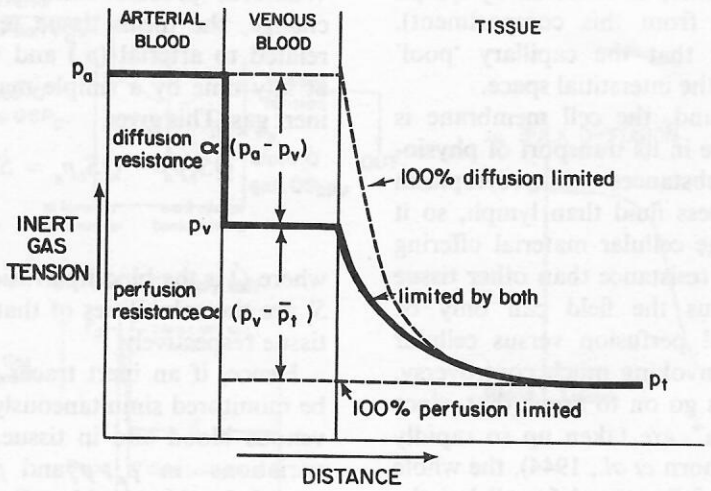

Fig. 57 Illustrating how the inert gas tension of venous blood (p_v) will equal that of arterial blood (p_a) for a system in which blood–tissue exchange is controlled by diffusion and how it will equal the mean tissue value ($\bar{p}_t$) for a purely perfusion-limited system. When both processes control gas exchange, it can be seen how the relative proximity of p_v to p_a or $\bar{p}_t$ provides an index of their relative preponderance

but the venous tension (p_v) may be regarded as the best attainable approximation. Should it approach closer to the arterial (p_a) than the average tissue tension ($\bar{p}_t$), then this would be a good indication that diffusion was rate-limiting; otherwise it must be perfusion.

In other words, during uptake, arterial blood has the highest tension and tissue the lowest with venous lying somewhere in between (fig. 57). Thus the $(p_a - p_v)$ differential reflects the perfusion limitation relative to $(p_v - \bar{p}_t)$ representing the diffusion gradient; so that, for a totally circulation-limited system, venous blood leaves in equilibrium with tissue giving an infinite ratio for $(p_a - p_v)/(p_v - \bar{p}_t)$ since $p_v = \bar{p}_t$ for that extreme case.

Unfortunately no set of results could be found in which arterial, venous and average tissue tension had all been measured directly with increasing time. Most tissue tensions have been estimated by arterio-venous difference using Equation 58 expressed as an integral between limits set by ambient and initial conditions. Estimating λ by chemical means, and determining $\dot{Q}$ by direct mechanical measurement of total brain blood flow, $\bar{p}_t$ can be estimated as a function of time from the mass balance equation (58). The fact that their curves for $\bar{p}_t$ (fig. 58) for some subjects lay very close to the corresponding p_v curves has been offered by Kety and Schmidt (1945) as strong evidence in favour of a perfusion-limited system. However, in determining $\bar{p}_t$ curves by this method, they make no allowance for the arterio-venous difference which must occur simply on account of blood residence time. Incumbent blood must be first displaced from a tissue before a tracer can appear on the venous side, even if there is no extravascular uptake. It is necessary to postulate a mean blood residence time of only 30 sec in order to obtain a separation of $\bar{p}_t$ from p_v equal to that between p_v and p_a after 10 min. However, the sojourn of blood in brain is not likely to reach 30 sec but is probably closer to 8 sec. Even so, the unfortunate fact emerging from arguments such as these is that the interpretation of arterio-venous data requires an accurate assessment of a small difference between two very large quantities, where this difference can also be influenced by technical problems in measuring blood flow mechanically and in estimating any collateral circulation.

Some check on the whole method is afforded by the time constants for inert gas uptake (k in Table 9) which Kety and Schmidt also determine from their data using Equation 59. If nitrous oxide uptake in the brain is almost totally perfusion limited, as indicated by the very close proximity between p_v and $\bar{p}_t$ obtained by mass balance (fig. 58), then their time constants derived from Equation 59 should give a very good prediction of $\dot{Q}$.

These calculations have not been included by Kety and Schmidt but values of $\dot{Q}$ estimated from their data by this other method (Equa-

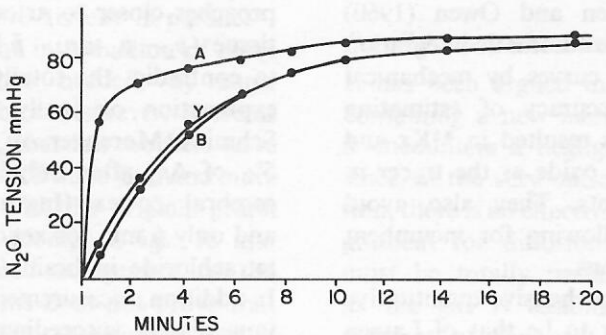

Fig. 58 The uptake of nitrous oxide by the brain of a monkey. A: arterial N_2O tension; Y: venous N_2O tension; B: mean brain N_2O as estimated by mass balance (Equation 58). Redrawn from Kety and Schmidt (1945)

Table 9 Comparison of cerebral blood flow ($\dot{Q}$) determined from the same experiments for the uptake of nitrous oxide by brain and calculated: (1) from the time constant (k in Equation 59), (2) by arterio–venous difference (Equation 58) and (3) by direct measurement (data from Kety and Schmidt, 1945)

Time constant in min^{-1}	Tissue: blood partition ($1/\lambda$)	Cerebral blood flow ($\dot{Q}$) in ml (g tissue)$^{-1}$ min^{-1}		
		(1) k/λ (perfusion controlling)	(2) by a–v balance	(3) by direct measurement
0·182	1·3	0·24	0·36	0·37
0·198	1·6	0·32	0·35	0·42
0·102	1·0	0·10	0·22	0·17
0·154	1·4	0·22	0·42	0·46
0·287	1·3	0·38	0·62	0·60
0·089	1·3	0·12	0·30	0·31
0·266	1·4	0·37	0·36	0·38
0·230	1·5	0·34	0·66	0·76
0·138	1·2	0·17	0·34	0·32

tion 59) based on a perfusion-limited system are given in column (1) of Table 9. However, they offer a very poor correlation with columns (2) or (3). Moreover, the fact that values derived on the basis of Equation 59 are *smaller* than the true flow rate is an indication that diffusion may be playing a significant role in controlling blood:tissue exchange. Even so, the coincidence between p_v and $\bar{p}_t$, together with the correlation between columns (2) and (3) in Table 9, are much quoted in favour of gas uptake in brain being perfusion limited.

Isotope studies

The basic Kety and Schmidt method has been modified by Lambertsen and Owen (1960) who essentially introduce automatic integration of arterial and venous curves by mechanical means. The greater accuracy of estimating radioactive isotopes has resulted in ^{85}Kr and ^{133}Xe replacing nitrous oxide as the tracer in more recent experiments. They also avoid earlier objections by allowing for incumbent blood in their integrations.

By far the most comprehensive quantitative treatment would appear to be that of Lassen and Munck (1954) who incorporate terms to allow for the uptake of krypton by tissue following a bimodal curve, in addition to making a residence time correction. They must be very close to obtaining a true mass balance irrespective of which process predominates.

Incorporating these corrections into their methods of analysis of their data for uptake, Lassen and Klee (1965) derive mean brain tensions ($\bar{p}_t$) which they plot against time. They also plot the corresponding arterial (p_a) and venous (p_v) values from which they were computed, a typical time course taking the form shown in fig. 59.

However, these curves now show that, although venous and mean tissue tensions almost coincide at the start of uptake, their time courses soon diverge. In fact, after only 2–3 min of ^{85}Kr elimination, venous approaches closer to arterial than it is to mean tissue ($p_a - p_v < p_v - \bar{p}_t$) which would appear to contradict the totally perfusion-controlling explanation originally offered by Kety and Schmidt. Moreover Δp_v approaches to within 5% of Δp_a after only 5 min for krypton in cerebral cortex (Ingvar and Lassen, 1962) and only 6 min for xenon or 5 min for carbon tetrachloride in brain (Pittinger *et al.*, 1956). In addition, measurements of ^{85}Kr elimination, immediately succeeding those for 10 min of uptake, confirm that equilibrium between venous blood and tissue could not have been attained in this period (Lassen and Klee, 1965).

At first sight, these data may appear to

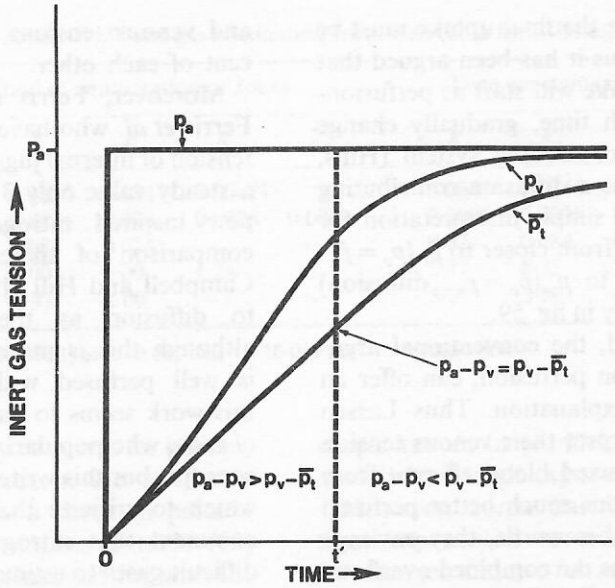

Fig. 59 Typical curves for the uptake of various radio-isotopes by whole brain, showing simultaneous levels for arterial blood (p_a), venous blood (p_v) and mean tissue ($\bar{p}_t$). t' refers to the time that p_v becomes closer to p_a than to $\bar{p}_t$. Redrawn from Lassen and Klee (1965)

demolish the concept that perfusion is the sole rate-limiting process. However, the perfusion-controlling concept was already too well established and its mathematical simplicity too popular for it to be challenged by the time these more accurate isotope data became available. Moreover, it could be shown to be compatible with the conventionally accepted view by postulating more 'tissues' in parallel—exactly analogous to the introduction of more 'Haldane tissues', when needed, by some designers of diving tables. However, it seems to this writer, at least, that few workers have realized the degree to which these later and more accurate data conflict with the original graph of Kety and Schmidt (compare figs. 58 and 59) which really gained acceptance of the perfusion argument. This does not prove that they were wrong in their conclusion but if available at the time, these data might have left the perfusion : diffusion issue open. Hence the Kety and Schmidt argument, much quoted in favour of a circulation-controlling system, must be regarded as inconclusive in the light of more recent data.

If these recent uptake data are now analysed without preconceived ideas, then two parallel lines of reasoning can be developed, one based on perfusion and the other on diffusion, with each being sufficiently compatible with the evidence for neither to be an obvious choice.

Parallel interpretations

It has been argued that when the first blood containing a new inert gas enters a capillary, it encounters a negligible diffusion resistance since, at the very outset of this *transient* situation, there is an effectively infinite concentration gradient for diffusion. Hence initial uptake, must be totally perfusion limited. However, as the gas is assimilated, its concentration gradient at the wall will fall rapidly, thus increasing the diffusion resistance (see fig. 57). Towards the end, on the other hand, there is a virtually negligible gradient at the blood: tissue interface, yet increasing towards more

remote regions where the final uptake must be diffusion limited. Thus it has been argued that the limitation to uptake will start as perfusion-controlling and, with time, gradually change over to a diffusion-controlling system (Hills, 1970c). By this means a diffusion-contributing model can provide a simple interpretation for the switch-over of p_v from closer to $\bar{p}_t$ ($p_v = \bar{p}_t$: perfusion) to closer to p_a ($p_v = p_a$: diffusion) as depicted graphically in fig. 59.

On the other hand, the conventional argument, based purely on perfusion, can offer an equally acceptable explanation. Thus Lassen and Klee (1965) interpret their venous tension as representing the mixed blood efferent from at least two tissues, one much better perfused than the other. In other words, they envisage mixed venous blood as the combined overflows from two 'tanks' in parallel. This explanation for the variation in p_v in the jugular vein is perfectly reasonable for an organ such as whole brain which is comprised of well perfused grey matter and poorly perfused white matter along with lesser amounts of other tissues. Thus simultaneous measurements of arterial and venous tensions, with subsequent estimation of mean tissue by mass balance, can be equally well interpreted by either a mixed perfusion : diffusion model or by one based on heterogeneous perfusion.

Direct tissue analysis

Any uncertainty in estimating mean tissue tension ($\bar{p}_t$) from arterio-venous differences (Equation 58) can be avoided by direct tissue analysis for gas, the only set of such directly determined tissue tensions which the writer could find being those of Campbell and Hill (1933). They cut out the organs of goats electrocuted before decompression from three, four and five atmospheres gauge pressure of air and obtained the following half-saturation times for nitrogen:

brain	—	4 hours
liver	—	3 hours
bone marrow	—	4 hours

These times are several orders of magnitude greater than the periods required for arterial and venous tensions to come within five per cent of each other.

Moreover, Ferris and Engel (1951) quote Ferris *et al.* who have shown that the nitrogen tension of internal jugular venous blood reaches a steady value only 3 min after changing to a new inspired nitrogen partial pressure. A comparison of these figures with those of Campbell and Hill (1933) undoubtedly points to diffusion as the rate-limiting process; although this is more likely in brain since it is well perfused with blood. Unfortunately this work seems to have escaped the attention of those who popularized the perfusion-limiting concept; but this writer can find no grounds on which to criticize their results other than to comment that nitrogen is one of the more difficult gases to estimate by analysis.

Although the above evidence relating p_a to p_v to $\bar{p}_t$ may appear conflicting, it leaves little doubt that no one organ is either a simple stirred tank of the type depicted in fig. 56(a) or a simple membrane system (fig. 56(b)), both of which give a simple exponential response and a single time constant (Equation 59). Hence a more complex situation must be faced where both processes control transfer simultaneously or blood perfusion is grossly heterogeneous in reality.

Simultaneous uptake of different gases

One means of overcoming this ambiguity in interpretation is offered by monitoring the simultaneous uptake or elimination of two or more inert gases. This approach exploits the difference in time constant (k) for a uniformly perfused tissue, i.e. $k = \lambda \dot{Q}$ (Equation 38) if it is 100% perfusion-limited compared with

$$k \propto D \propto 1/\sqrt{(M_w)} \qquad (60)$$

where D is the diffusion coefficient of the gas which is related to its molecular weight (M_w) by Graham's law of diffusion. Thus it should be a simple matter to compare time constants (k values) for two or more inert gases and then see whether they lie in the ratios predicted by Equation 38 for perfusion or by Equation 60 for diffusion.

This approach has essentially been taken

Table 10 Analysis of inert gas elimination from man (data from Jones, 1951)

Gas	Method of enumeration of Jones					Time constants in order of extraction				
	k_1	k_2	k_3	k_4	k_5	k_1	k_2	k_3	k_4	k_5
N_2	0·46	0·087*	0·024†	0·0047‡	—	0·0047‡	0·024†	0·087*	0·46	—
Xe	0·35	0·987	0·024	0·0038	0·0008	0·0008	0·0038	0·024	0·087	0·35
He	0·50	0·084	0·024	—	—	0·024	0·084	0·50	—	—
Ratio (N_2/Xe)	1·32	1·00	1·00	1·24	—	5·87	6·32	3·62	5·29	—
Ratio (He/N_2)	1·09	0·97	1·00	—	—	5·11	3·50	5·74	—	—

Nitrogen values given by Behnke (1951) are: *0·085 min^{-1}, †0·019 min^{-1}, ‡0·0054 min^{-1}.

by Jones (1951) who analyses curves for helium, nitrogen, krypton and xenon. He attributes each exponential term to a tissue in parallel with others and then compiles a table (10) in which he compares k values starting with the 'fastest' (highest k value) which he has extracted for each gas. The values in each column are similar and this he claims as major evidence in favour of blood perfusion as the rate-controlling process. This conclusion has been very widely quoted as supporting the use of Equation 59 and hence the conventional decompression theory based upon a multiplicity of simple tissues in parallel, each described adequately by a single exponential function.

However, Jones has listed an average of three exponential constants for helium, four for nitrogen and five for xenon. If these are now re-tabulated (Hills, 1966) in the order in which they *must be extracted* by backward projection (as employed by Jones—see fig. 60), so that the slowest terms for each gas are compared with each other, then the next slowest, etc., the same data is easier to correlate by Graham's Law, i.e. by Equation 60 rather than Equation 38 and thus supports control by diffusion

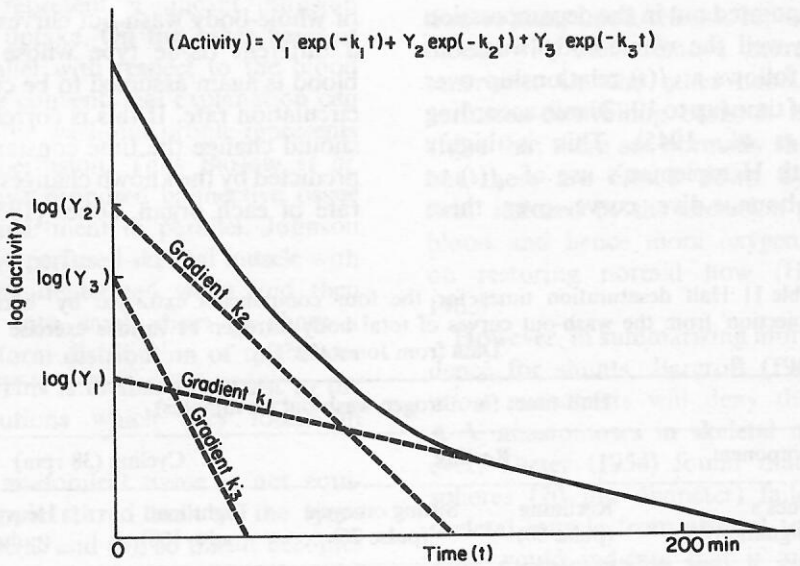

Fig. 60 Illustrating the process of 'backward projection' for extracting the exponential components, including both time constants (k_1, k_2, etc.) and coefficients (Y_1, Y_2, etc.) from a wash-out curve such as the one shown above for the elimination of ^{85}Kr from skeletal rabbit muscle

(see right-hand side of Table 10). The latter order of enumeration is also consistent with a bulk diffusion mechanism by which the expression for any model, e.g. Equation 83 shows the first and dominant term ($n = 1$) to be the 'slowest' (lowest k value). Thus the work of Jones would seem equally compatible with either a perfusion- or a diffusion-controlled system and should not be quoted as favouring exchange limitation imposed by the circulation—as seen frequently in the decompression literature.

Later studies of the wash-out of anaesthetic gases have avoided the above ambiguities in the method of enumerating time constants insofar as they obtained equal numbers of terms for all gases (Rackow *et al.*, 1965). When their data for different gases could not be correlated by Equation 59 on the basis of a simple perfusion model, they invoked gross inter-tissue diffusion to explain the discrepancies (Perl *et al.*, 1965). However, the introduction of so many combinations of interfaces and factors describing their relative proportions, provides so many more degrees of freedom that there is then insufficient data to test the adequacy of the model.

It is seldom pointed out in the decompression literature how well the whole-body wash-out of inert gases follows a $\sqrt{(t)}$ relationship over short periods of time (up to 10–20 min according to Eggleton *et al.*, 1945). This is highly compatible with Hempleman's use of $\sqrt{(t)}$ to describe the bounce-dive curve over these intervals (p. 122) and, hence, with the concept of bulk diffusion into a single tissue responsible for limb bends. However, in reviewing mathematical analysis of wash-out curves in general, Hennessy (1973a) points out that both perfusion and diffusion models predict similar asymptotes, while the curves for small time intervals would enable us to differentiate much more easily. Unfortunately, these are the regions where the experimental error is greatest and factors such as the delay imposed by the lungs (fig. 55) can obscure the subtle differences being sought.

Exercise

To return to the work of Jones (1951), since he is one of the few workers widely quoted in the decompression literature by those in favour of retaining simple 'Haldane tissues', another means of settling this vital issue is afforded by varying $\dot{Q}$, when k should change on a perfusion basis (Equation 38) but not on a diffusion basis (Equation 60)—unless there is also vasodilation to change the 'geometry'. Thus Jones and others have interpreted each of the exponential terms found by his analysis of whole-body wash-out curves as representing a different tissue type whose exchange with blood is again assumed to be controlled by the circulation rate. If this is correct, then exercise should change the time constants in a manner predicted by the known changes in the perfusion rate of each organ. Jones (1951) repeated his

Table 11 Half desaturation times for the four components extracted by 'backward projection' from the wash-out curves of total body nitrogen at various exercise levels. Data from Jones (1951)

	Half-times for nitrogen wash-out (in minutes)			
Component	Resting		Cycling (38 rpm)	
(Jones's designation)	Reclining (pulse 60)	Sitting on cycle (pulse 76)	Light load (pulse 108)	Heavy load (pulse 114)
I	1·50	2·15	1·08	0·80
II	8·00	5·95	7·95	2·85
III	29·5	23·7	14·7	14·4
IV	147·0	147·5	135·0	163·0

wash-out curves for the same subject resting, sitting on a bicycle and then cycling at various known rates. However, none of the time constants of the various components increased by a factor of more than 2·8 in going from rest to heavy exercise (see Table 11), compared with a known increase of at least 20-fold in the perfusion rate of skeletal muscle. Since this tissue type makes the major contribution to body weight, its component could not have been missed and this would add strong evidence for a significant diffusion contribution in limiting blood : tissue exchange.

Single tissue uptake

According to Jones's argument, the problem of allotting the various exponential terms needed to characterize whole-body wash-out to specific organs should be avoided if simply one tissue is studied. However, taking skeletal muscle as the most uniform, even this tissue gives a multi-exponential wash-out (fig. 60). This indicates that this tissue is not effectively one fully-stirred 'pool' but consists of various compartments. If these compartments lie in series, then their boundaries or some of their contents must represent significant diffusion barriers to gas uptake. On the other hand, if they lie in parallel with respect to the blood supply, then the conventional explanation can be offered that the wash-out profile represents heterogeneous perfusion. Thus Barlow *et al.* (1959, 1961) have proposed connective tissue as a gross compartment in parallel. Johnson *et al.* (1952) have perfused skeletal muscle with blood containing deuterated water and then actually cut it into small dices to show a moderately uniform distribution of this tracer upon analysis. This is in sharp contrast to the uneven distributions which they found in liver and brain.

Hence each anatomical tissue is not equivalent to a simple stirred tank of the types shown in figs. 56(a) and (b), so that it becomes a meaningless exercise attempting to correlate body tissues with 'Haldane tissues'.

Shunts

There is a large literature on reactive hyperaemia in skeletal muscle in which isotope clearance data have been interpreted assuming total control of transfer by perfusion, i.e. using Equation 59. If blood flow to a limb is cut off for a short time by pressing on an artery then, upon release, flow is higher than normal for a few minutes to enable the tissue to 'pay off' the 'oxygen debt' accrued by the tissue. Measurements of isotope clearance during this manoeuvre shows that, naturally, it stops during occlusion but then proceeds more rapidly after release, more or less in step with the increased blood flow. However, if the artery is released more gradually so that the restored flow is not allowed to exceed normal, it is found that when isotope clearance is resumed it does not follow a line with the same gradient as before—as predicted for the same blood flow ($\dot{Q}$) in Equation 59 describing a totally perfusion-limited system. Rather, the relative clearance rate is increased (fig. 61) to rejoin an extrapolation of the original rate before occlusion.

The first explanation is simply that, in a diffusion-limited transport system, the tracer will continue to be transferred to the incumbent blood in which it will accumulate during occlusion so that, upon release, replacement of this blood will then remove more tracer than otherwise. On the other hand, on a purely perfusion-controlling basis, it is necessary to argue that there are normally shunts in muscle but these are closed down by the 'oxygen debt' induced by the occlusion to divert more blood and hence more oxygen to the tissue on restoring normal flow (Hyman *et al.*, 1963).

However, in summarizing morphological evidence for shunts, Barcroft (1963) states that 'most anatomists will deny the existence of A–V anastomoses in skeletal muscle'. Moreever, Dieter (1954) found that small plastic spheres (20 μm diameter) failed to traverse skeletal muscle from arterial to venous sides. This would indicate that if any direct A–V shunts exist then their diameter and hence their blood-carrying capacity must be very limited. Current opinions on this matter seem to reflect the views of Zweifach (1949) that, in skeletal muscle, there are vessels connecting

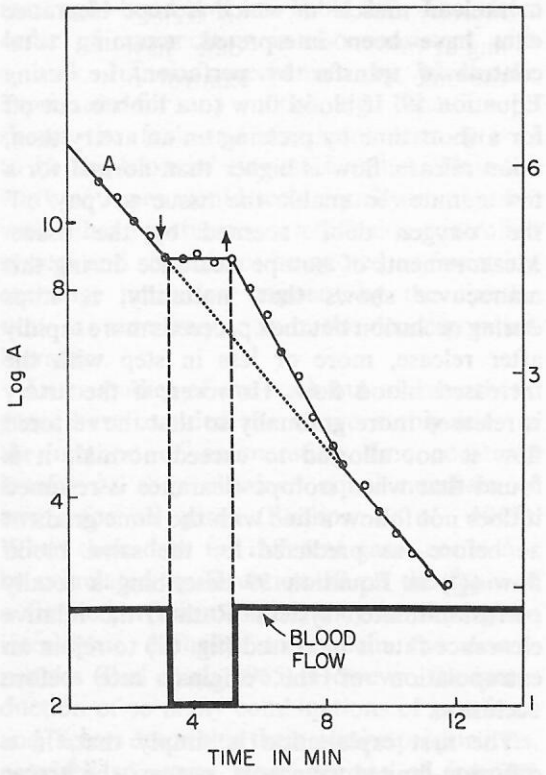

Fig. 61 Tissue content of a radioisotope, measured as its activity (*A*), plotted during washout from a muscle when the blood flow is interrupted and then restored to the previous level rather than to the natural level which would normally be greater by virtue of reactive hyperaemia. Data from Hyman *et al.* (1963)

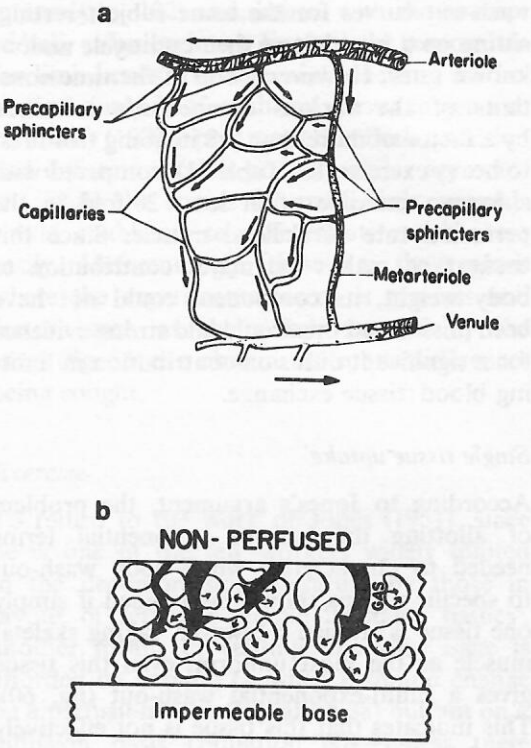

Fig. 62 (a) A schematic diagram of the microcirculation in skeletal muscle. The concept of Zweifach (1949). (b) The 'two-phase' concept of excised tissue (Hills, 1967b) envisaged as cells of uniformly low permeability immersed in an extracellular medium in which diffusion—and hence uptake—is much more rapid

arterioles to venules of larger calibre than capillaries but it is questionable whether these have the flow capacity to be termed shunts (see fig. 62(a)).

There are much more data which could be cited here but most of it is even less pertinent to this vital issue than the foregoing example in that it can be equally well interpreted by either a perfusion- or a diffusion-controlling model.

Sympathetic stimulation and controlled flow

The real problem in attempting to sort out the perfusion–diffusion confusion is that an increased clearance can be attributed either to increased blood flow on a perfusion model or, on a diffusion model, to a change in the geometry of the tissue arising by virtue of the accompanying vasodilatation. However, if the latter can be controlled in an isolated muscle preparation by known stimulation of the sympathetic nervous system, a clear differentiation can be made when blood flow is changed; but blood flow must be changed extracorporeally by non-physiological means. Thus Renkin (1955, 1959, 1967) has devised a classical preparation on the near-isolated gastrocnemius muscle of the dog in which blood perfusion is controlled externally. He chooses to express his results in terms of the clearance (χ) which Renkin then relates to the 'capillary permeability' (Ξ) according to the following equation derived by Kety (1951):

$$\chi = \frac{\dot{Q}(c_a - c_v)}{(c_a - \bar{c}_t)} = \dot{Q}[1 - \exp(-\Xi A/\dot{Q})] \quad (61)$$

where c_a, c_v and $\bar{c}_t$ are the arterial, venous and mean tissue concentrations of the tracer and A is total capillary surface area in unit volume of tissue. Hence the clearance is the effective volume of blood which would be needed to equilibrate with tissue. Thus, if there were no diffusion resistance (when $c_v = \bar{c}_t$) and hence the capillary wall and all extravascular tissue were infinitely permeable ($\Xi = \infty$), then $\chi = \dot{Q}$ in Equation 61, i.e. all blood flow is effective in blood : tissue exchange. This is shown in fig. 63 along with the other limiting case of a totally diffusion-limited system where the permeability (Ξ) is small and hence the clearance (χ) is independent of blood flow.

In practice the clearance is found to follow neither extreme case but to be perfusion-limited at low flow rates and diffusion-limited at high flow rates as described earlier (see also fig. 57). Using tracers of different diffusibility such as antipyrine, radio-rubidium and urea, the smaller molecules tend to reach a plateau sooner as the blood perfusion is increased. Renkin has not been primarily concerned with the perfusion: diffusion controversy but applying the equation he uses for analysis to his data (Equation 61) would suggest that the major limitation to uptake *in skeletal muscle* is imposed by blood perfusion. However, Equation 61 has a number of hidden assumptions for use in clearance analysis which have been listed in a critical assessment by Hills (1970c). The major shortcomings concern the absence of time as an independent variable on the right-hand side of Equation 61, particularly for an expression describing what is essentially a *transient* situation. The second is the assumption that all diffusion resistance is confined to the capillary wall. This is reasonable in the popular use of this equation in studies of the large particles maintaining fluid homeostasis (Landis and Pappenheimer, 1963) but unduly favours perfusion when used to analyse clearance data for smaller molecules.

Thus Renkin's experimental data show that there is a significant diffusion resistance in skeletal muscle under normal physiological conditions. This is further demonstrated when he reduces the sympathetic stimulation (reduces

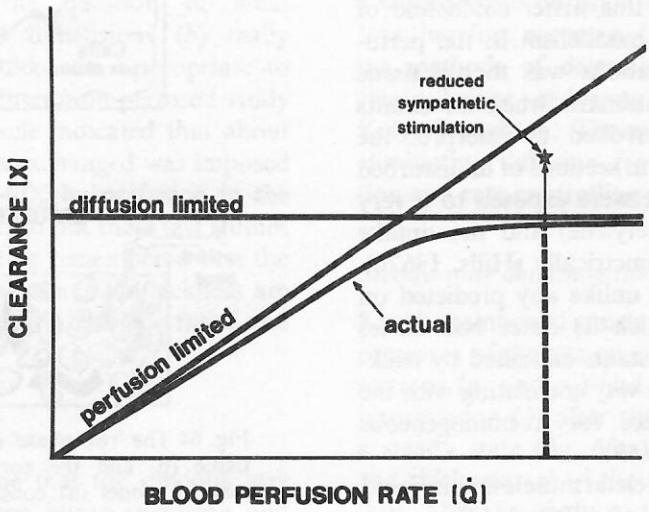

Fig. 63 The clearance of a tracer from the isolated hind-leg of a cat at a fixed rate of externally controlled sympathetic stimulation. This is plotted against known perfusion rates selected by an external means and is compared with the 'actual' value for the normal physiological state of that muscle. Redrawn from Renkin (1955)

vasoconstriction) at the same blood flow ($\dot{Q}$). The clearance increases, indicating the recruitment of more patent capillaries and hence a more favourable tissue geometry for exchange by diffusion (see fig. 63).

This ideal preparation devised by Renkin has been used specifically to study the perfusion: diffusion confusion by Vann *et al.* (1976). In a number of ingenious switches of both blood flow and tracers while monitoring the simultaneous uptake and clearance of two isotopes, they have shown a significant diffusion contribution to a predominantly perfusion-limited system—in skeletal muscle.

Those advocating a totally perfusion limited system, however, can always invoke more shunts to explain the deviations from their model so, just as it is never possible to disprove that last unlikely 'Haldane tissue' which can always be hypothesized to save the day for supersaturation, the situation returns to yet another analogy to the controversy between Copernicus and the believers in the Ptolemaic model of planetary motions (p. 166).

Excised skeletal muscle

About the only way this writer could find of avoiding the eternal parallelism in the perfusion/diffusion explanations was to use tissue from freshly killed animals, when no shunts could possibly be invoked to interpret the data. Thus thin uniform sections of undisturbed skeletal rabbit muscle were exposed to a very soluble inert gas (acetylene) and the uptake was monitored dilatometrically (Hills, 1967b). The time course was unlike any predicted on the uniform slab which its outer boundaries portray, the time constants extracted by backward projection in no way correlating with the 1 : 9 : 25 ratio sequence for a homogeneous medium (see Equation 49).

This suggests that skeletal muscle is composed of at least two media of different diffusivities. If these correspond to the two tissue regions listed earlier (p. 168) as the two most likely to differ in their permeabilities, then the most general two-phase model (fig. 62(b)) consists of:

(1) a continuous extracellular medium with the permeability of water through which gases can diffuse rapidly from the surface of the slab; and

(2) cellular material of uniform yet lower diffusivity dispersed evenly on the macroscale, the cells having irregular shapes.

Thus, at each depth of penetration of tissue by gas there is competition between the gas passing on deeper into the extracellular phase and that entering the nearest cell. When formulated mathematically, this model seems to offer an adequate interpretation of the data for gas uptake by the excised muscle slab (Hills, 1967b, 1968c). The interesting feature is the low value of 0·58 min^{-1} for (D_c/b^2) where D_c is the cellular diffusion coefficient and $2b$ is the effective cell diameter.

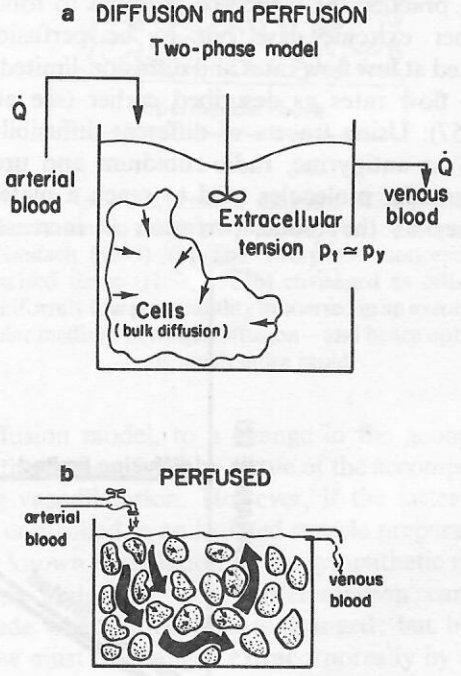

Fig. 64 The 'two-phase' concept of perfused tissue (b) and the corresponding mathematical model (a) consisting of a cell of uniformly low permeability, yet of irregular shape, immersed in an effectively fully stirred bath of extracellular fluid continuously perfused by the circulation. Thus the overall uptake is controlled by both cellular diffusion and extracellular perfusion as processes lying in series (Hills, 1966)

If ^{85}Kr uptake is measured in the same muscle before it is excised, much the same cellular constants (e.g. the same 'shape factor') can be derived if it is assumed that, in the living state, only extracellular tissue is effectively fully stirred (fig. 64). Any perfusion by blood is then restricted to this compartment. Thus it is implied that the low value derived for (D_c/b^2) in excised tissue also holds in the living state, implying that cellular material is several orders of magnitude less permeable than water (Hills, 1966, 1967b). However, justification for the model is not so convincing if one checks the author's use of a diffusion coefficient for acetylene in water which was taken from a handbook by Perry (1950) who misquotes a value from Arnold (1930). Even so, this approach avoids any chance of invoking shunts or other parallel A–V pathways to explain away results which do not conform to the simple perfusion model.

Higher values for (D_c/b^2) have been proposed on the basis of modifications to this two-phase model but, in their analysis, Tai and Chang (1974) omitted the interaction between cellular and extracellular fractions at each depth of penetration.

Before pursuing the question of what diffusivities (D_c) and dimensions (b) really apply to cells, it would seem appropriate to mention that the perfused/non-perfused study of skeletal rabbit muscle indicated that about 60–70% control of gas exchanged was imposed by diffusion and 30–40% by perfusion in the resting state. However, to put these last studies in perspective, it must be remembered that the critical tissue(s) in decompression sickness are probably not muscle but a lesser perfused and less vascular tissue.

Diffusion Times

Anyone might imagine that the obvious way to differentiate between blood perfusion and diffusion would be simply to calculate the time it would take for gas to diffuse from the blood into tissue. The distribution of patent capillaries, their distances apart and the dimensions of cells are known; while the relevant transcendental functions are readily available from several standard mathematical texts on heat conduction (Carslaw and Jaeger, 1959) and diffusion (Crank, 1956).

Hence one of the major arguments put forward by advocates of blood perfusion for the rate-limiting process is their estimation that mean extravascular tension should attain 95–99% of the asymptote within 1–5 sec of a step in blood tension of the same solute. This is so rapid that Kety (1951), Thompson *et al.* (1958) and Roughton (1952) have concluded that radial diffusion from a capillary should make no significant contribution in controlling blood : tissue exchange.

At first sight this would appear a most convincing argument, annihilating any claims that uptake is limited even in part by diffusion. However, in their calculations, these authors have employed values of diffusion coefficients which are either those for the same solute in water or those determined from excised tissue sections by steady-state methods, often using values derived by Krogh (1918). However, it was pointed out that the use of *steady-state* values in *transient* equations only retains any physical meaning if tissue can be regarded as a *homogeneous* diffusion medium (Hills, 1966). It is therefore necessary to take a close look at the methods of determining diffusion coefficients before endorsing the conclusions of Kety, Roughton, Thompson and others and eliminating diffusion from further consideration as a rate-controlling process.

Steady-state determinations of diffusivities

Krogh maintained constant yet different partial pressures of the gas on either side of his tissue sections (p_1 and p_2) and measured the rate of transmission ($\dot{q}$) after the system had reached a steady state (fig. 65(a)). Knowing the area and thickness (x) of the tissue section, he was thus able to deduce the overall diffusion coefficient (D) from Fick's law as

$$D = \dot{q}x/AS(\Delta p) \qquad (62)$$

Krogh actually derives a permeability (DS/x) but the quoted dimensions enable D to be

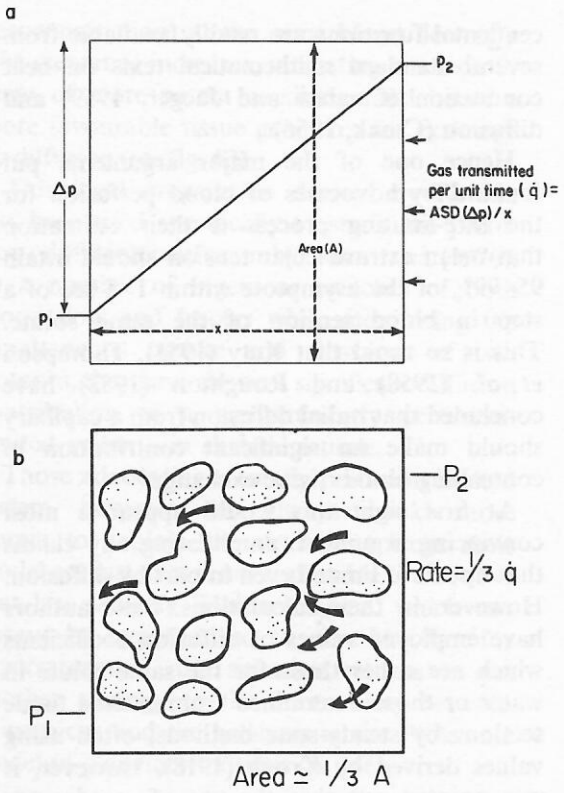

Fig. 65 (a) Demonstrating Fick's law of diffusion for steady-state conditions in a homogeneous medium. (b) The same gas gradient $(p_2 - p_1)$ for a heterogeneous medium such as tissue—envisaged here as a case where much less permeable cells occupy two-thirds the total cross-sectional area (A) and so block transmission to reduce the effective diffusion coefficient of the same gas in water by roughly the same fraction

extracted from his data as about 10^{-5} cm^2 sec^{-1} at 37 °C. This is about one-third of the value for nitrogen in water at the same temperature (3×10^{-5} cm^2 sec^{-1}), yet many orders of magnitude larger than $D_c = 2{\cdot}2 \times 10^{-10}$ cm sec^{-1} derived from the value for (D_c/b^2) obtained from the excised muscle preparation described earlier.

Accordingly, there is either a gross error in the uptake data and/or the model used to derive D_c/b^2 on p. 180, or tissue is grossly heterogeneous in its permeability to gases. Thus it has been argued (Hills, 1966, 1967b) that an overall tissue diffusion coefficient one-third of that for the same gas in water is just what would be expected on the two-phase model, since two-thirds of the cross-sectional area of Krogh's tissue sections would be occupied by relatively impermeable cells (fig. 65b).

Thus, if tissue is really as heterogeneous as this work would indicate, then overall tissue values for D become almost meaningless in estimating uptake and elimination, since the cells possess most of the capacity of the tissue for assimilating inert gases in solution. This is therefore of particular importance to decompression optimization; so let us consider a simple thermal analogy, since the laws of conduction and diffusion correspond exactly.

Thermal analogy

Consider copper, containing lumps of asbestos, being cast into a parallel-sided slab. If the opposite faces are maintained at fixed yet constant temperatures to establish a *steady state*, the heat will take paths by way of the copper, so that any estimation of thermal conductivity from the heat passing across the block would give a value for copper reduced roughly by the proportion of the cross-sectional area occupied by asbestos.

On the other hand, if that block is now tossed into a bath of hot water and the overall heat uptake measured then, in this *transient* situation, transfer will now be dictated much more by the thermal conductivity of the asbestos, since this phase possesses most of the capacity for heat. Hence an overall thermal conductivity measured under the steady-state conditions of the first experiment would be virtually useless in determining the course of heat uptake by the composite block in the transient situation.

Without further labouring a simple point, the perfusion: diffusion controversy reduces to the necessity to accept either heterogeneous perfusion or the heterogeneous permeability of tissue. It is also interesting to note that, in describing his experiments, Krogh comments that it took much longer to reach steady state than he would have anticipated from the thickness of his sections. This observation is easily explained if cells are appreciably less permeable than tissue overall.

However, while it is reasonable to expect some degree of heterogeneity in the permeability of tissue, cellular diffusion coefficients need to be at least an order of magnitude or two lower than that of water for the diffusion times calculated by Kety, Roughton and Thompson to be revised to levels which would reverse their conclusions annihilating diffusion as a rate-controlling process (p. 181). Hence it is necessary to determine diffusion coefficients in *cellular* material.

However, before devising mathematical models to extract values of D_c from practical data, it is first necessary to know whether the cell should be treated as a medium of uniform permeability or just a well mixed bag in which the cell wall offers the only resistance to exchange between its contents and its external environment.

Mode of diffusion

Three-dimensional tissue models for tracer exchange have been proposed assuming a well stirred intracellular region and a less permeable cell membrane (e.g. Harris and Burn, 1949) and this would seem quite reasonable for the physiologically active solutes whose transport properties they were studying. As an example, the whole study of the active transport of Na^+ is based upon the cell membrane and its unique unidirectional transmission properties. However, this should not apply to inert solutes which would be transferred by passive diffusion in accordance with Fick's law and the other laws of passive transfer.

The experiment from which it is easiest to extract the cellular diffusion coefficient with the minimum of ambiguity in the model is probably that of Fenichel and Horowitz (1963). They saturated the readily separated fibres of the frog sartorious muscle with various tracers. This fibre bundle was then rapidly transferred to a well stirred bath containing fresh saline in which they monitored the tracer as it was eliminated from the cells.

The wash-out was found to be multi-exponential (analogous to fig. 60) and the time constants for the first two components, i.e. the predominant terms, were found to lie in the ratio corresponding to diffusion into a long uniform cylinder (Equation 83). This is particularly interesting, since it indicates that the resistance to wash-out was provided by bulk diffusion within the muscle fibre as a homogeneous medium rather than its elimination simply being restricted by a relatively impermeable cell membrane. It is very difficult to interpret the multi-exponential wash-out of inert tracers simply on the basis of the distribution in fibre diameters of membrane-limited cells.

Hence the mode of uptake appears to be bulk diffusion. This is unfortunate in some respects, since it complicates the mathematics so that it is no longer feasible to use compartmental analysis (Robertson, 1962) and hence linear systems analysis so convenient in programming most models for the computer (Milhorn, 1966; Milsum, 1966). However, having established the mode of diffusion, an attempt can now be made to extract the diffusion coefficient of this effectively uniform cellular material—cytoplasm plus cell membrane.

Cellular diffusion coefficients

Unfortunately cells are too small for a section simply to be cut and the diffusion coefficient for cellular material (D_c) measured by the steady-state method used by Krogh for whole tissue (Equation 65). The few very large cells that do occur in several invertebrates have such a highly developed endoplasmic reticulum that they are effectively two-phase anyway, so it is doubtful whether any values derived from these could be applied to mammalian tissue. It therefore becomes necessary to employ *transient* methods to determine D_c, but this, as mentioned earlier, leads to more complex mathematical extraction of the answer from the data.

Upon analysis, transient methods do not yield D_c directly but a group of constants (D_c/L^2) with the dimensions of $(\text{time})^{-1}$, where L is a characteristic length used in the mathematical model—such as a capillary radius (a) or an intercapillary distance ($2b$). What is quite remarkable is the extent of agreement

Table 12 Comparison of cellular diffusion time scales for nitrogen—mostly from Hennessy (1973a)

Mathematical model	Source	Dc/a^2 min^{-1}	Data analysed
Linear diffusion	Hempleman (1969)	0·00321	decompression
Non-linear gas resistor	Weaver (1967)	0·00376*	decompression
Cylindrical interaction	Hennessy (1973a)	0·00423	†
Radial diffusion	Hills (1969d)	0·00516‡	decompression
Linear interaction	Hills (1967b)	0·00538§	muscle uptake

*Equivalent diffusion constant computed by Hennessy (1973a).
†A more sophisticated analysis using data from the other sources.
‡Mean value.
§Based on acetylene data, with Graham's law correction.

in the values for (D_c/b^2) for nitrogen, considering the widely differing models and the different sources of data from which they were derived. Hennessy (1973a) has compiled a table (see Table 12) of these values. Apart from models already described, this table includes a value derived from analysis of the Canadian 'series' pneumatic decompression meter (p. 129) whose empirical modifications have led to a system which, according to Hennessy (1973b), closely simulates radial diffusion.

This close agreement between values of (D_c/b^2) for nitrogen taken from both diving and laboratory data for uptake is reasonable until values of about 10^{-3} cm (10 μm) are substituted for b (see Table 13), when $D_c = 7 \times 10^{-11}$ cm^2 sec^{-1}. This is a staggering $1{\cdot}3 \times 10^5$-fold smaller than the Krogh steady-state value of 10^{-5} cm^2 sec^{-1}. Even if $b = 20$ μm, which is large for a muscle fibre, at least, the ratio (D_c/D) is still of the order of 3×10^{-5}.

Thus, to interpret these values of (D_c/b^2)

Table 13 Capillary density, capillary surface, and maximum diffusion distance in various tissues. Data from Kety (1951)

Tissue	Species	Capillary density no. per mm^2	Capillary surface cm^2/cm^3	Maximum diffusion distance μm
Muscle	frog	400	190	28
Muscle	horse	1400	240	15
Muscle	dog	2600	590	11
L. ventricle	human	5730	1090	8
R. ventricle	human	5680	1080	8
Vent. septum	human	4450	850	8
Papillary muscle	human	5220	990	8
Heart muscle	mouse	5300	1000	8
Cerebral cortex	human	1000	190	18
Cerebral cortex	mouse	1250	240	16
Cerebellum	mouse	1700	330	14
White matter	human	300	57	33
Adipose:				
fat-rich	rat	274	52	34
fat-poor	rat	1000	222	18
Liver	mouse	4200	800	9
Duodenum	mouse	2400	460	11
Pancreas	g. pig	1900	360	13
Renal cortex	mouse	4500	850	8
Renal medulla	mouse	7400	1400	7

determined by truly *transient* methods, it is necessary to postulate either a cellular diffusion coefficient 10^{-5} times smaller than that for the same gas in water; or an intercapillary distance ($2b$) of the order of 1–2 cm.

However, no tissue is this avascular, so the prospect arises of either accepting a cellular diffusion coefficient (D_c) for nitrogen which is smaller than that of water by a staggering factor of about 10^{-5} or dismissing such values as impossible. Before making any decision, this would seem an opportune moment to consider what values have been determined for substances other than gases.

D_c values for non-gaseous solutes

One means of avoiding much of the uncertainty introduced in the use of a mathematical model and the need for validation is provided by the experiment of Fenichel and Horowitz described earlier (p. 183). In the case of their separated muscle fibres, whose diameter ($2b$) can be measured directly, there is no doubt about the value for b or the relevant model. Hence it is most significant that they derived diffusion coefficients for twelve inert solutes, each value being appreciably lower than that for the same solute in water (D_w). Their values gave the ratio (D_c/D_w) varying from 3×10^{-2} to 10^{-6} and it is most significant that this range covers the ratio of 7×10^{-6} for nitrogen.

Other cells

Turning to cells other than muscle fibres, Dick (1959) summarizes the uptake of deuterated water by some 23 different cell types. To avoid assuming that the cell membrane has the same permeability as cytoplasm, he depicts each result as the locus of the permeability of the cell wall (Ξ) to the diffusion coefficient of cytoplasm (D_c). These loci are shown for the 19 types of intact cell in fig. 66. If the conclusions of Robertson (1959) are accepted—that all cell membranes have similar basic structure and hence similar water permeabilities, while the diffusional properties of the cell interior are also basically similar, then the lines in fig. 66

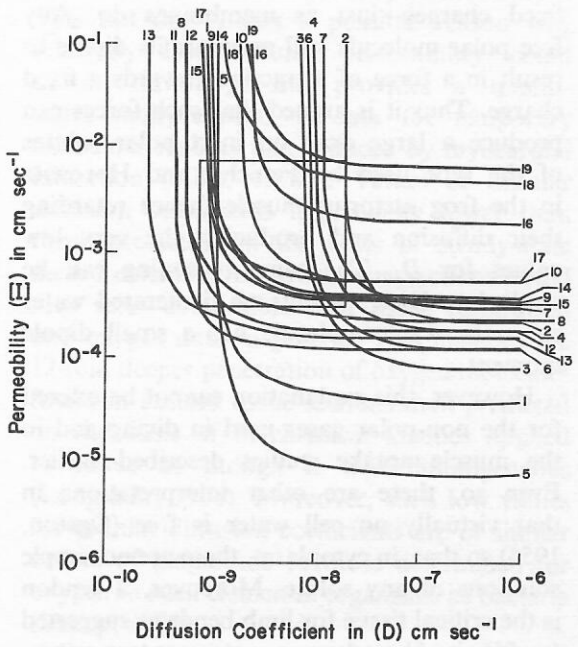

Fig. 66 The permeability coefficient of deuterated water (Ξ) in cell membrane and its diffusion coefficient (D) in cytoplasm; each line depicts a single undissected cell and represents possible combinations of Ξ and D which fit the experimental data. The square outlines the smallest range of common values which would fit the behaviour of them all. Redrawn from Dick (1964)

should pass through a common locus. As Dick (1964) points out, this is not necessarily a point, since no two cells are identical but can be depicted by the square shown in fig. 66. This now limits the range of diffusion coefficient for this wide variety of cell types to 8×10^{-10} to 2×10^{-8} cm^2 sec^{-1}. Comparison of these values with that for deuterated water in free solution at the same temperature ($D_w = 2{\cdot}4 \times 10^{-5}$ cm^2 sec^{-1}) gives values for the (D_c/D_w) ratio ranging from $8{\cdot}3 \times 10^{-4}$ to $3{\cdot}3 \times 10^{-5}$.

Yet again, therefore, cytoplasm appears to be many orders of magnitude less permeable than water.

Explanation for low permeability

Fenichel and Horowitz interpret their low

cellular diffusion coefficients at the molecular level on the basis that cytoplasm contains fixed charges—just as membranes do. Any free polar molecule will orientate its dipole to result in a force of attraction towards a fixed charge. Thus it is argued that such forces can produce a large drag on inert polar solutes of the type used by Fenichel and Horowitz in the frog sartorius muscle, hence retarding their diffusion and producing the very low values for D_c. The same reasoning can be applied to Dick's results on deuterated water since the water molecule has a small dipole moment.

However, this explanation cannot be offered for the non-polar gases used in diving and in the muscle uptake studies described earlier. Even so, there are other interpretations in that virtually no cell water is free (Ogston, 1956) so that, in cytoplasm, there are no simple solutions of any solute. Moreover, if tendon is the critical tissue for limb bends as suggested (p. 56), its fibres have a water content appreciably lower than most aqueous tissues with values for man variously estimated from 70% (Rollhauser, 1950) to as low as 58% (Lowry *et al.*, 1941).

This raises the question of whether diffusion coefficients of the order of 7×10^{-11} cm^2 sec^{-1} are likely from a purely physical standpoint and how these values compare with permeabilities in non-biological media. A survey of the physics literature indicates a very interesting similarity between crystalline materials and the two-phase concept of tissue proposed earlier (p. 180) to interpret Krogh's steady-state measurements on gross tissue sections. In crystals, the solute is transmitted predominantly by way of the imperfections, diffusion into the true crystallites (analogous to cells) proceeding at a rate which is 10^{-5} to 10^{-10} times slower (Shewmon, 1963).

Recalculation of diffusion times

The foregoing discussion has presented a reasonable case for not dismissing very low cellular diffusion coefficients; although some may find it incredible that, in this day of modern technology, no non-mathematical method is available to differentiate between values of 10^{-5} and 7×10^{-11} cm^2 sec^{-1} for D_c. However, if the calculations of diffusion times performed by Kety (1951), Roughton (1952) and others are now repeated using the same equations but a diffusion coefficient of 7×10^{-11} cm^2 sec^{-1} in place of Krogh's steady-state value of 10^{-5} cm^2 sec^{-1}, nitrogen half-saturation times of the order of 1–4 hours are now obtained (Hills, 1966). This is comparable to the nitrogen half-saturation times determined experimentally by Campbell and Hill (see p. 174) and is very difficult to match by any of the known blood perfusion rates of tissue (see Table 14).

Table 14 Blood perfusion rate of human tissue

Organ	Blood perfusion* (ml/100 gm/min)	Implied time constant (k) in min^{-1}†
Thyroid	560	5·6
Kidney/liver	150	1·5
Heart	100	1·0
Intestine	70	0·7
Brain	65	0·65
Spleen	40	0·4
Stomach	25	0·25
Hand	7–12	0·07–0·12
Finger	15–40	0·15–0·4
Forearm (muscle)‡	1–3	0·01–0·03
Leg (muscle)‡	1–2	0·01–0·02

*from Bell, Davidson and Scarborough (1961).
†assuming an aqueous tissue and density of 1·0 gm ml^{-1} ($\lambda = 1$ in Equation 38).
‡Resting values.

The estimation that diffusion times may be much longer than first calculated using the Krogh value now suggests that we might reverse the earlier decision that diffusion is not rate-controlling. Thus the last and strongest point so often quoted in favour of perfusion-limited blood : tissue transfer would seem to be equally compatible with control by diffusion. However, very low values for the cellular diffusion coefficient for gases raises other criticisms.

Oxygen diffusion

Nitrogen and oxygen are two gases of similar

molecular weight (28 compared with 32) and both are non-polar, so the diffusion coefficient which applies to one should be little different for the other. Hence the argument can be raised against low values for D_c (Hills, 1970d) to query why the body should tolerate such a low cellular permeability of oxygen when it is essential to metabolism and the well-being of each cell. However, before attempting to answer this question, it should be pointed out that cells with a high oxygen demand, such as muscle fibres, contain myoglobin which is known to facilitate intracellular diffusion by chemical means—as much as four-fold in some cases (Wittenberg, 1970).

The same two-phase model used for interpreting data for the transient uptake of inert gases (fig. 62(b)) has been applied to the steady-state assimilation of oxygen by tissue sections (Hills, 1970d). This has given a ratio of cellular to extracellular oxygen diffusion coefficients of the same low order as that found for nitrogen although, as Gold and Longmuir (1971) point out, the value of D_c extracted from this analysis is hyperdependent upon the value taken for the respiration rate. In fact, it could be as high as overall tissue values in liver sections.

This criticism is supported by an ingenious determination of the clearance of a gaseous isotope from flat excised tissue sections undertaken by Evans *et al.* (1974). They conclude that the cellular diffusion coefficient of xenon must be greater than $2{\cdot}2 \times 10^{-8}$ cm^2 sec^{-1} compared with an overall tissue value of $3{\cdot}8 \times 10^{-6}$ cm^2 sec^{-1}—still heterogeneous to the extent that D/D_c may exceed 172. However, their study again refers to liver, so the vital experiment needed would appear to be one of repeating their measurements on tendon, but the practical difficulties encountered so far in this laboratory leave no doubt why most experimentalists prefer to work with liver.

To return to the question of oxygen, one possible advantage of a low diffusion coefficient for oxygen in cells is that those closest to the local oxygen source, i.e. to circulating blood, would not compete so successfully for oxygen molecules and hence would leave more to be transmitted to more remote regions of the tissue. These are, therefore, more likely to survive a transient insufficiency of blood flow. This not only offers a possible reason why relatively low cellular permeability could be an advantage but provides a quantitative interpretation of data for temporary ischaemia such as that induced by myocardial infarction (Hills, 1970d). Values of cellular diffusion coefficients appreciably lower than those predicted on the basis of steady-state measurements across gross tissue sections would thus seem compatible with tissue respiration and oxygen data in general. This includes the 12-fold deeper penetration of oxygen molecules found in excised tissue sections than predicted on the basis of biochemical kinetics applied to tissue as though it were homogeneous (Longmuir, 1966). Moreover, such low values for cellular diffusion coefficients are of similar orders of magnitude to those determined for oxygen in such elemental organisms as bacteria (Shoup, 1929).

Consequently, the 'oxygen' counter-argument to low cellular diffusion coefficients for nitrogen is difficult to substantiate. However, before seeing what evidence there is of diffusion limitation in practical diving, it will be as well to summarize the more academic aspects of this vital issue.

Academic aspects of perfusion versus diffusion

The popular belief that blood perfusion is the only process effectively controlling blood : tissue gas exchange would seem open to re-appraisal. The four pieces of evidence most quoted in favour of this concept would seem to be adequately interpreted on a diffusion basis. These are:

(1) the Kety and Schmidt experiment (p. 171) based on the comparison between p_a, p_v and $\bar{p}_t$;

(2) the data of Jones (p. 175) for the simultaneous elimination of different inert gases;

(3) the estimation of diffusion times by Kety (1951), Roughton (1952) and others; while another argument aimed more specifically against low values for D_c is

(4) the 'oxygen' argument against low diffusion coefficients for non-polar gases in cells.

Even though each of these points and others can be countered on a diffusion basis, however, any designer of decompression tables must be apprehensive about using a cellular diffusion coefficient 10^{-5} times smaller than gross tissue values without some practical indication from decompression studies.

Decompression Studies

Academic studies of the perfusion: diffusion controversy tend to suffer from the problems common to other vital issues—notably whether any conclusion can be applied to the unidentified tissue(s) responsible for marginal bends. The faster onset of bends when diving on heliox compared to air (p. 33) is an indication of some rate-controlling contribution by diffusion. However, it can easily be argued that this refers to a growth or coalescence process which occurs *after* the primary event and is therefore not relevant to the process inducing it. There are two decompression studies which largely avoid such criticisms.

Nitrogen versus helium for bounce dives

The safe exposure limits for no-stop decompression offer a unique means of studying the mode of uptake of the inert gas by the critical tissue(s), particularly when these bounce-dive curves are compared for different gases. These have the fundamental advantages of effectively isolating gas transfer from the other vital issues and the many accompanying uncertainties surrounding gas elimination during gradual decompression. Thus, in bounce diving, gas *uptake* only is being considered, in which case the selection of nitrogen or helium as the inert gas reduces to a 'trade-off' between the lower solubility of helium which is less soluble than nitrogen by a factor of 1·5 in aqueous tissue and 3·3 in fat and the faster diffusion of helium, D_c being 2·7 times greater for helium than nitrogen, if uptake is purely diffusion limited.

Thus for long 'bottom' times, where the diver is approaching a steady state, solubility factors dominate and helium should always be superior to nitrogen. This is certainly confirmed by the greater minimum bends depth for 80:20 helium:oxygen than for air (p. 193); although there is some indication to the contrary for aerial decompression (Beard *et al.*, 1967). This solubility advantage should also apply for shorter exposures if uptake is controlled entirely by blood perfusion. On the other hand, if diffusion is rate-limiting, then the 2·7-fold faster diffusion of helium should outstrip its 1·5 solubility advantage over nitrogen, so that air would then be superior for short exposures.

This line of reasoning has been offered by Hempleman (1967) in his comparison of bounce-dive curves determined on goats for both air

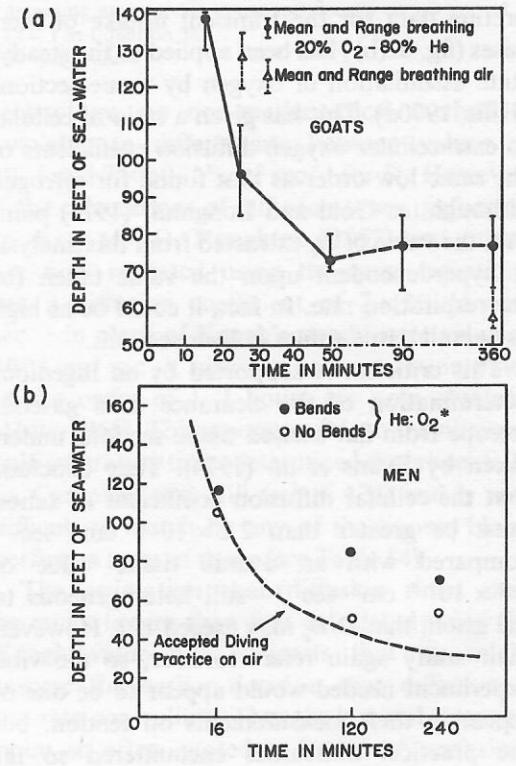

Fig. 67 Comparison of the bounce dive (no-stop decompression) curves for air and heliox (a) with 80:20 $He:O_2$ on goats and (b) with values for 90:10 $He:O_2$ adjusted to the equivalent depth for 80:20 $He:O_2$ on the basis of equal P_{He} and compared with the standard air curve of Van der Aue *et al.* (1951). Note the indication that the air and heliox curves intersect. Redrawn from Hempleman (1967)

and 80 : 20 helium : oxygen mixtures. His data indicate that the curves for the two mixes intersect (fig. 67(a)) indicating that nitrogen is better than helium for no-stop (bounce) dives of duration less than 20 min. The same also appears to hold for men if Hempleman's data for 90 : 10 helium : oxygen is theoretically adjusted to the equivalent pressure of 80 : 20 for equal inspired P_{He} (fig. 67(b)). Hence this experiment offers support for a significant limitation of the rate of inert gas uptake imposed by diffusion. Moreover, Hempleman goes on to point out that in order to explain this result by blood perfusion, it would be necessary for the very fast 'Haldane tissues' to have a helium : nitrogen solubility advantage of 1 : 3, i.e. to be predominantly lipid. Thus the 5- and 10-min 'tissues' of the 'Haldane' perfusion model would need to be fatty tissues; but these are usually avascular and have much lower perfusion rates than any which could provide a 5- or 10-min half-saturation time. At least this is the general belief, although blood perfusion rates ranging from 10 ml/100 ml per min in inguinal fat to 27 ml/100 ml per min in interscapular brown fat have been reported in various adipose tissues—but in rats (Herd and Goodman, 1966).

Thus this classical experiment of Hempleman offers quite strong evidence that an appreciable degree of control of gas uptake *in the critical tissue(s)* is provided by diffusion.

Empirical helium and nitrogen functions

In deriving decompression schedules, the time course for gas assimilation is almost invariably represented by a mathematical function, either one adopted for its simplicity such as the exponential, or one synthesized to describe a particular model. This is depicted by $\phi(t)$ in Equation 26. However, there is a totally different approach; simply using diving data to derive the time course empirically. Bounce-dive data (no-stop decompression limits) are particularly convenient for this type of 'analytical' derivation of $\phi(t)$ versus t since most of the vital issues are then avoided. At least, the use of *one* equation, e.g. Equation 26, does assume that only *one* 'tissue' is involved.

This 'analytical' line of deduction has been used to derive the empirical time-courses for both nitrogen and helium which were then compared with various 'synthetic' mathematical functions to conclude that a radial diffusion model offered the best 'fit' (Hills, 1969e). However, the extraction of the empirical $\phi(t)$

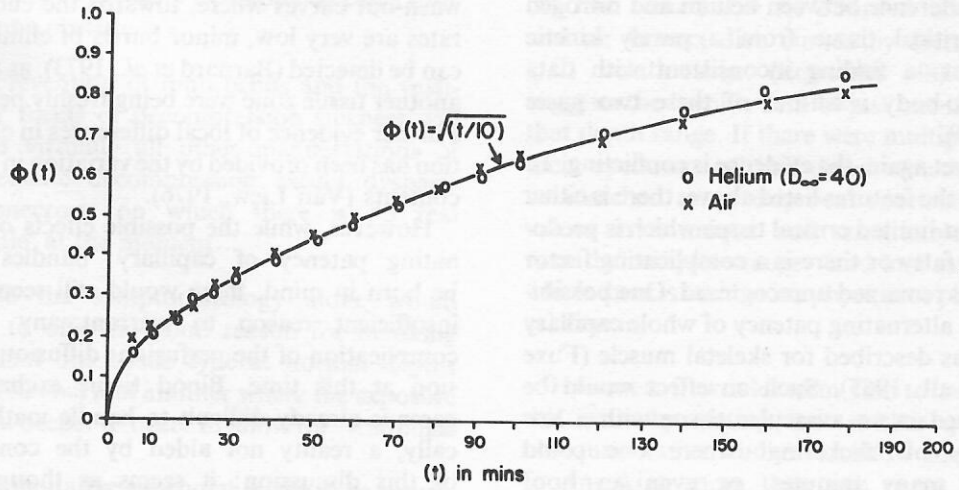

Fig. 68 Empirical time functions for the uptake of nitrogen and helium by the bends-provoking tissue extracted from the experimental 'bounce dive' data of Van der Aue *et al.* (1951) for nitrogen and of Duffner (1958) for helium by use of Equation 26. Redrawn from Hills (1975a)

for helium uptake did not allow for the simultaneous wash-out of nitrogen in using bounce-dive data recorded by Duffner (1958).

This correction has been made recently in an analysis which first determines $\phi(t)$ for nitrogen from the standard air bounce-dive curve of Van der Aue *et al.* (1951), *assuming* the critical tissue to be aqueous (p. 193). This empirical function is then used to estimate nitrogen elimination during the simultaneous uptake of helium in the no-stop decompression dives of Duffner *et al.* (1959) to give the true empirical $\phi(t)$ for helium after allowing for simultaneous nitrogen : helium separation according to Equation 31. The empirical functions for both gases are shown in fig. 68. These show two very clearly defined features:

(a) the empirical helium and nitrogen functions almost coincide—a point strongly favouring perfusion limitation in view of the difference in diffusion coefficients for nitrogen and helium;

(b) both empirical time functions follow Hempleman's $\sqrt{(t)}$ relationship (Equation 48) very closely—a point strongly favouring diffusion limitation, since all bulk diffusion equations reduce to this form for small values of t (Hills, 1966).

The curves in fig. 68 indicate that, when divorced from solubility considerations, there is little difference between helium and nitrogen in the critical tissue from a purely kinetic standpoint—a finding inconsistent with data for whole-body wash-out of these two gases (Table 10).

Thus, yet again, the evidence is conflicting. To reconcile the features listed above, there is either a diffusion-limited critical tissue which is predominantly fatty or there is a complicating factor which has remained unrecognized. One possibility is the alternating patency of whole capillary bundles as described for skeletal muscle (Fuxe and Sedvall, 1965). Such an effect would be emphasized in an avascular tissue with a low frequency of 'flickering' where one could envisage many minutes, or even an hour elapsing before a particular region is perfused. Preliminary experiments in this laboratory, involving continuous I.V. infusions of India ink, show grossly heterogeneous perfusion of the frog Achilles' tendon, microscopic examination showing well perfused areas spanning 2–4 mm yet separated by 5–10 mm of tissue in which none of the carbon tracer could be seen. These distances are gradually reduced as fresh areas open up, yet some patches remain totally unperfused several hours after the start of the experiment. Alternating patency provides a convenient alternative to bulk diffusion in deriving $\sqrt{(t)}$ by stochastic theory but the prospect of such a complication to the model presents a nightmare to the designer of decompression tables.

Final comment

The concept of extensive zones of tissue randomly perfused during uptake but closed down for various periods during decompression until metabolic demands force them to re-open presents a difficult model by which to optimize the depth : time profile. It may add credence to a minority view that it is virtually impossible to avoid a certain minimal incidence of bends whatever decompression is prescribed. Over sufficient dives, some area of the critical tissue will fail to open and vent its dissolved gas until it is too late to avoid symptoms. Some indirect support for this view is found in gas wash-out curves where, towards the end when rates are very low, minor bursts of elimination can be detected (Barnard *et al.*, 1973), as though another tissue zone were being freshly perfused. Further evidence of local differences in elimination has been provided by the variation in bubble contents (Van Liew, 1976).

However, while the possible effects of alternating patency of capillary 'bundles' must be born in mind, there would still seem to be insufficient reason to warrant any further complication of the perfusion: diffusion confusion at this time. Blood : tissue exchange of gases is already difficult to handle mathematically, a reality not aided by the conclusion of this discussion: it seems as though *both perfusion and diffusion* exert a significant degree of control—at least over some period of a long decompression.

The Critical Tissue(s)

There are a number of features of the critical tissue type(s) which physiologists would like to know: These include

(a) their number, since this determines the number of equations to be used, i.e. the number of independent conditions to be satisfied by the decompression profile;

(b) their composition and any other physical features needed for the model; and

(c) their anatomical identity. This is not essential but it would help greatly in answering (a) and (b), while it would also make direct tissue monitoring a much more meaningful exercise.

Number of tissues

The anatomical identities of the likely tissues have been discussed earlier in connection with the mechanism (Chapter 3). However, as far as the symptomatology was concerned, there appeared to be two major features.

(a) There was no need to invoke more than one tissue type for limb bends and one for vestibular dysfunction; while cerebral symptoms can be explained by intra-arterial bubbles. Spinal lesions are probably associated with intravascular bubbles of some form, while the mechanism of aseptic osteonecrosis remains obscure.

(b) Prevention of limb bends and the vestibular forms of decompression sickness will avoid virtually all other manifestations of inadequate decompression except dysbaric osteonecrosis on which there is no real 'handle' at the moment.

Hence the symptomatology alone would appear to offer no good reason for invoking more than one tissue type at normal depths (up to 300 fsw) and another where the exposure has been deeper in order to allow for 'vestibular bends'.

This qualitative viewpoint seems to be consistent with quantitative studies which include:

(1) The experiment of Rashbass and Hempleman specifically designed to answer this question. This requires a linear H_1 versus H_2 relationship in fig. 47 for there to be just one relevant function and hence one tissue for limb bends as described on p. 154. This condition is essentially satisfied because the deviation at one end can be attributed to gas phase formation reducing gas elimination. This deviation only occurs *after* decompression.

(2) It has been argued (Hills, 1966) that if more than one tissue were involved, then there would be a transition point (kink) in the bounce-dive curve (no-stop decompression limits). Since none can be detected (figs. 12 and 67), it can therefore be deduced that no more than one function and hence *one tissue type* is involved, at least up to the depth limits at which it is practical to derive the bounce-dive curve.

(3) Above these limits, Hempleman (1975) has found evidence for a transition point in the P_1 versus P_2 relationship for decompression from steady state (fig. 20). When the exposure has exceeded a depth in the vicinity of 300 fsw for P_1, 'vestibular bends' become more prevalent and so another tissue then needs to be considered. This is again compatible with qualitative deduction.

(4) The remarkable fit afforded both heliox and air bounce-dive curves by Hempleman's $\sqrt{(t)}$ relationship (Equation 48) strongly suggests the involvement of just one tissue over that depth range. If there were multiple tissues, their spectrum of half-times would need to be matched to a reciprocal spectrum of 'M' values in a unique and remarkable manner over the complete range—and in a manner for which there is no obvious physical or physiological reason.

However, it would seem fair to summarize this issue by stating that neither qualitative nor quantitative studies can show good reason for invoking more than one tissue for limb bends and another where the exposure has exceeded 300 fsw—anatomical tissue types, that is.

CNS symptoms

The next and very difficult question concerns decompression sickness involving the CNS; whether further tissues need to be invoked in the calculation to allow for them. Cerebral or spinal manifestations can always be induced as the presenting symptom after an act of stupidity involving decompression well beyond a safe pressure but is seldom, if ever, the first indication on a marginal dive. Moreover, none of the quantitative exercises in varying exposure parameters listed in the previous section can produce cerebral and spinal decompression sickness as the marginal case in the same way that 'vestibular bends' become prevalent (see fig. 20). P. 70

At least, this is true for regular decompression. However, in the experiment depicted in fig. 54 it has been shown that the extent of the upward excursion briefly interposed between exposure and decompression largely determines the type of decompression sickness (Hills, 1971a)—at least, for an exposure of 170 feet for 30 minutes using U.S.N. tables. No overshoot, or one from 30 up to only 20 fsw, still produces limb bends as the marginal case when the total decompression time is gradually reduced on successive exposures. However, when the upward excursion is extended by a further 10–20 fsw, i.e. up as far as 10 feet or the surface and back, then the presenting symptoms are predominantly of the CNS variety, yet occur towards the end of normal decompression. This experiment has provided a very convenient model for studying Type II decompression sickness and its treatment in goats.

P. 164

This result has been interpreted on the basis that recompression to the first stop facilitates the release of bubbles filtered out of the venous system by the lungs. This is compatible with the view derived from the symptomatology that cerebral and possibly spinal symptoms arise from intravascular bubbles (Chapter 3). Hence, unless there is some unusual feature in the dive, such as an excessive upward excursion, then the prevention of extravascular gas should also prevent its subsequent escape into the vascular system and the provocation of CNS symptoms. In other words, unless non-innervated lipid tissues are depositing excessive gas into blood or some factor such as high carbon dioxide or chronic oxygen poisoning is impairing the filtering action of the lung, the prevention of limb and 'vestibular' bends should also prevent cerebral and spinal decompression sickness for a single straightforward dive. Hence there would not seem to be sufficient justification to add any further tissues to the two already considered necessary in the calculation of decompression profiles.

Constitution of the critical tissue

Several of the earlier conclusions relating to the perfusion: diffusion controversy were based on the assumption that the critical tissue is predominantly aqueous; but is this so? Philp and co-workers have frequently implicated lipids in the aetiology of decompression sickness (p. 55), while Workman (1969) has explained his very slow 'tissues' as adipose. There is much more theoretical implication of lipids which could be cited but there is also the practical fact that obese subjects tend to be more susceptible to decompression sickness (p. 41).

From an 'aqueous' standpoint, more obese subjects are likely to have more fatty inclusions in tissues which are still predominantly aqueous, e.g. in tendon (p. 59). Blood lipids are likely to play a role in chronic decompression sickness but once again it is difficult to see how recompression could provide such an immediate and effective treatment if bubbles were not the primary factor—at least in the acute stages.

The fact that intravascular bubbles have been observed to enter the circulation from lipid tissues does not confirm these as responsible for marginal symptoms. The argument has been pursued in some detail on p. 147 that these tissues may be so expanded with gas during decompression that they may even rupture, spilling their contents into blood, yet would not give pain since they have virtually no nerve endings to signal their injury. This could explain the correlation between Doppler

sounds and decompression ratio (Pilmanis, 1976), but not so well related to the bends incidence (p. 146).

Qualitative arguments such as these can be followed almost endlessly without reaching any decision relevant to the composition of this unidentified critical tissue responsible for marginal limb bends. Thus there is a need to revert to more quantitative evidence to try to settle this issue.

Firstly, no lipid tissue is sufficiently well perfused for blood to convey sufficient gas to allow that tissue to give rise to symptoms after the very short exposure times at the 'deep end' of the bounce-dive curve. This certainly applies on a perfusion-limiting basis, where 'tissues' are needed with 5-min and 10-min half-times in the 'Haldane' method. Moreover, it was the conclusion of the 'analytical' study of the kinetics of nitrogen and helium uptake (p. 189) that a fatty tissue would need to be diffusion-controlling which, in turn, would require perfusion rates to be even higher for the circulation not to control blood: tissue exchange.

Different inert gases

The conditions most likely to emphasize any involvement of fatty tissues are those where kinetic factors are virtually eliminated by reaching a steady state before decompression, i.e. allowing enough time for fat to equilibrate with the alveolar partial pressure of the inert gas. Moreover, a switch to another inert gas with a different solubility ratio between lipid and aqueous tissue should enable us to differentiate.

This line of reasoning has been essentially followed by the Oxford group (Lever *et al.*, 1971a) who have undertaken a very large number of decompressions of mice using six inert gases of widely differing solubilities and fat/aqueous solubility ratios (S_f/S_a). These include nitrogen, helium, argon, nitrous oxide, carbon tetrafluoride and sulphur hexafluoride.

No single blend of lipid and water from 100% of one to 100% of the other offers a correlation of the data for all gases. However, the best fit is provided by fat from which they conclude that 'the most important single factor governing the appearance of decompression sickness seems to be the excess gas in solution in fatty tissue'. The only major deviation is helium. However, this study used mice and hence severe CNS symptoms—if not death itself—as the indication of decompression sickness, an end point criticized by many, including Powell (1972a). Moreover, it is difficult to extrapolate from death in mice to marginal limb bends in man. Incidentally, the implication of a lipid tissue by Lever *et al.* is consistent with the earlier discussion that disruption of fatty tissues would provide intravascular bubbles responsible for the CNS symptoms and hence those observed in the Oxford mice.

Marginal limb bends

To return to marginal limb bends in man, marginal decompression from three steady-state situations can be compared which are as well established as any available.

(1) The minimum bends depth for air diving is usually taken as 33 fsw for a 'weak' diver; only 13% 'bend' at lesser depths (Crocker *et al.*, 1951).

$$[P_1 = 66 \text{ fsw}, P = 33 \text{ fsw}, S_a = 0{\cdot}0125 \text{ atm}^{-1}, S_f = 0{\cdot}069 \text{ atm}^{-1}]$$

(2) The minimum bends depth on 80 : 20 helium : oxygen for this incidence of limb bends is about 40 fsw but could be rather lower—anywhere down to 38 fsw according to the data of Duffner (1958).

$$[P_1 = 71\text{–}73 \text{ fsw}, P = 33 \text{ fsw}, S_a = 0{\cdot}0095 \text{ atm}^{-1}, S_f = 0{\cdot}017 \text{ atm}^{-1}]$$

(3) The minimum bends altitude for decompression from air breathing has been placed at 23,000 feet for 13% incidence in a large group of cadets (Gray, 1944b) i.e. an absolute pressure of 307 mm Hg (13·33 fsw).

$$[P_1 = 33 \text{ fsw}, P = 13{\cdot}33 \text{ fsw}, S_a = 0{\cdot}0125 \text{ atm}^{-1}, S_f = 0{\cdot}069 \text{ atm}^{-1}]$$

It is very fortunate that (1) and (3) refer to an identical incidence of bends. The unknown fraction of fat (f) in the critical tissue can be related to the decompression defined by P_1 and P and solubilities of the gas in fat (S_f) and aqueous tissue (S_a) by eliminating S_{N_2} and m' from Equations 27, 28 and 47. After substituting $P_w = 47\,\text{mm Hg} = 2{\cdot}04\,\text{fsw}$ and $F_{IN_2} = 0{\cdot}8$, this gives

$$fS_f + (1-f)S_a = v(P+c)/(0{\cdot}8\,P_1 - P - c - 1{\cdot}63) \qquad (63)$$

where c is a constant defined by

$$c = B - m \qquad (64)$$

Hence there are three unknowns: f, v and c and three sets of data, so it is possible to solve Equation 63 to obtain $c = 5{\cdot}1$ fsw and then

either $f = 0{\cdot}023$ and $v = 0{\cdot}0047$ for P_1 (He) = 73 fsw

or $f < 0{\cdot}01$ and $v = 0{\cdot}0043$ for P_1 (He) = 71 fsw

Thus, whatever reasonable value is taken for P_1 for 80 : 20 helium : oxygen, this simple calculation indicates that the critical tissue for limb bends is predominantly aqueous and probably contains less than 3% lipid. It would be necessary for the minimum bends depth for heliox to exceed 80 fsw for it to be a fatty tissue. Hence the quantitative data would appear to be in basic agreement with the qualitative deduction that the tissue responsible for Type I decompression sickness is predominantly aqueous.

Decompression from steady state

Having derived the above values, it is interesting to go back and see whether they are compatible with data for the very simple case of a single decompression from a steady state at P_1 to a new absolute pressure P_2—see p. 120. If the above figures are substituted into Equation 45, the gradient (W) for the P_1 versus P_2 relationship can be derived for air diving as $(0{\cdot}0045 + 0{\cdot}0125)/0{\cdot}0125 \times 0{\cdot}8 = 1{\cdot}71$ for an aqueous tissue—which agrees well with an experimental value of 1·76 derived from Hempleman's data (fig. 35) for goats (Hills, 1966). By comparison, the use of a fat solubility for nitrogen (0·069) would give a predicted gradient of 1·065.

An analysis similar to the derivation of Equations 43 and 45 has been performed by Hennessy and Hempleman (1977) to derive the P_1/P_2 gradient as $(1 + v/S)$ for *normoxic* diving. Substitution of the above values for v and S_{He} gives a value of $1 + (0{\cdot}0045/0{\cdot}0095) = 1{\cdot}47$ for an aqueous tissue or $1 + (0{\cdot}0045/0{\cdot}017) = 1{\cdot}26$ for a fatty tissue. Their experimental value extracted from the normoxic helium data of Barnard (1975) is 1·397—a figure closer to the 'aqueous' prediction and yet not close enough to be conclusive.

However, Hennessy and Hempleman use a lower minimum bends altitude (about 18,000 feet), lower minimum bends depth (about 29 fsw) for air and their own values for helium decompression to derive their constants. These, combined with the use of rather different Bunsen coefficients, such as $S_a = 0{\cdot}0087$ for water and $S_f = 0{\cdot}0150$ for olive oil, compared with $S_a = 0{\cdot}0095$ and $S_f = 0{\cdot}0170$ quoted overleaf, cause a sufficient variation to yield a P_1/P_2 gradient of 1·361. The proximity of this predicted value to the experimental (1·397) therefore leads these authors to the reverse conclusion, viz. that the critical tissue for limb bends is fatty.

Some readers may dismiss this whole section as another case where mathematics can prove almost anything; but such calculations still provide one of the few methods for tackling such fundamental problems. However, it does emphasize the need to check very carefully the equivalence of values for minimum bends depth and minimum bends altitude before employing them in this type of analysis.