On the role of separated gas in decompression procedures

BY H. B. GRIFFITHS, K. W. MILLER, W. D. M. PATON, F.R.S.
AND E. B. SMITH

Department of Pharmacology and Physical Chemistry Laboratory,
University of Oxford

(Received 2 March 1971)

(i) Experiments have been made on the incidence and time of onset of decompression sickness in mice exposed in single or repeated exposures to raised pressures of nitrogen or helium. If a first (conditioning) exposure to pressure is followed 5 min later by a second (test) exposure, the incidence of sickness is considerably higher than that for either exposure alone, or for a single exposure equal in length to the sum of the other two exposures. The same result is obtained if the conditioning exposure is to saturation. Sickness produced by repeated exposures has a shorter latency of onset than after single exposures. These results are explicable on the basis of asymptomatic bubble formation after decompression.

(ii) This latent susceptibility to decompression sickness, as revealed by the test exposure, initially increases with time after decompression, reaches a maximum, and then declines. The rate of decline is faster than can be accounted for on the basis of the decay and local reabsorption of bubbles. It is suggested that gas bubbles are also removed by passage from the tissues through the venous system to the lungs.

(iii) The degree to which very short second exposures to pressure (lasting only a few seconds) give rise to the symptoms of decompression sickness cannot be explained on the basis of the kinetics of bubble growth. These symptoms could also arise from compression by the second exposure of bubbles in the tissues, allowing them to enter the venous system and pass to the lungs, where, if expanded by decompression before elimination, they give rise to severe decompression sickness.

(iv) These observations are in direct conflict with the principles on which current decompression tables are based. The relative success of the latter must be attributed to the empirical manner in which the tables have been constructed and modified in the light of experience. The results support the theory that separated gas may be present in symptomless decompressions and raise the question of gas transport to the lungs as a factor which should be taken into account in the design of decompression tables.

INTRODUCTION

Any theory upon which decompression schedules are based must make two general postulates. First it must define a critical condition which, if it is exceeded, will lead to decompression sickness, and second it must put forward mechanisms by which gas is taken up, distributed and released by the body. The bases of all modern decompression tables are the principles laid down by Haldane over 50 years ago (Haldane, Boycott & Damant 1908). He observed that there was a pressure, about 2 ata, at or below which man can remain for long periods and then return to normal pressures rapidly without symptoms. He took this to indicate that the body could tolerate a certain degree of supersaturation. He then noted that, from Boyle’s and Henry’s laws, the same volume of gas could be released for the same proportionate fall in pressure, and suggested that a safe procedure would be one in which the ratio of the dissolved gas partial pressure to the final
external pressure was always less than a critical value of about two. Haldane further suggested that the body may be regarded as made up of a number of tissues perfused with blood at various rates, each saturating and desaturating reversibly with a characteristic half-time. If the inert gas partial pressure in any tissue exceeded the critical ratio the procedure was taken to be dangerous.

Whilst some modern decompression tables are still based directly on these ideas, others have found it necessary to make empirical modifications to Haldane's assumptions. Thus it was deduced by Hempleman (1960, 1969) from double dive experiments that the release of gas from tissues was slower than the corresponding uptake. This irreversibility was incorporated into the calculation of the decompression tables and was ascribed to interference with elimination of gas by the presence of non-symptomatic bubbles, the so-called 'silent bubbles'. Furthermore, Hills (1970) has gone so far as to suggest that any degree of supersaturation gives rise to silent bubbles and that conventional schedules are in fact treating a gas phase in the tissues rather than preventing the separation of gas from solution. Though difficult to test quantitatively, preliminary evidence indicates that the procedures based on Hills's ideas may be more satisfactory than those customarily employed.

A test of the assumptions of such models, particularly those of the Haldane type, is provided by the experiments described in this paper, using double dives. The first or conditioning dive is followed after a period at 1 ata by a second or test dive which provides a measure of the latent risk induced by the first dive. Thus, if the time between two identical dives is increased, any Haldane-type model, as well as the model of Hills if instantaneous (thermodynamic) equilibrium is assumed, would predict that the incidence of decompression sickness after the test dive would monotonically decrease. Our results show that, on the contrary, under a variety of conditions the incidence of decompression sickness actually increases as the time between the two dives increases.

**Methods**

Male white mice (Tuck C.D. strain no. 1) were used. Lever (1969) has demonstrated a relation between the weight of these mice and the incidence of decompression sickness after a given exposure. In this work only mice weighing 25 to 27 g have been used. The animals were allowed unrestricted feeding up to the time they were used. The signs of decompression sickness in mice usually occur within 12 min of decompression. They are: gradual loss of muscle 'tone', respiratory difficulty leading to generalized convulsions and collapse, usually followed, after a period of stupor, by death. The incidence of decompression sickness was taken as the fraction of mice that die within a definite period of time, usually 15 min. No attempt was made to assign scores to mice exhibiting marginal symptoms since this would have required continuous surveillance and subjective judgement. The time of onset of the sickness was taken as the first convolution.
Role of separated gas in decompression procedures

The mice were exposed in groups of five or six in a cylindrical pressure vessel provided with three viewing ports and of internal dimensions 12 cm x 26 cm. A thermocouple monitored the chamber temperature which was maintained at 29 to 31 °C by circulating thermostatted water in an outer jacket. The mice were supported on a 13 mm mesh wire platform above a tray of soda lime. A powerful fan, driven by an induction motor, mixed the chamber gases, and the carbon dioxide level was maintained at 0.012 atm (9 mmHg). At the beginning of each experiment and immediately after decompression, oxygen was flushed through the chamber. The oxygen partial pressure was thus maintained close to 1 atm, the inert gas pressure was equal to the gauge pressure, and after hyperbaric exposures the animals were eliminating dissolved inert gas into a pure oxygen atmosphere. Pressures are expressed in the actual number of atmospheres of a particular gas, e.g. 10.2 atm N₂. Since 1 atm of oxygen was always present, the total absolute pressure is given by the inert gas pressure plus 1 ata. Compression and decompression were achieved rapidly. Decompression was completed in about 10 s. The decompression procedures used are severe by human standards; but they give rise to no pulmonary barotrauma (Lever, Miller, Paton & Smith 1966), and the Haldane ratio is known to vary with the size of the animal, being about 11 for mice, 3 for goats (Hempleman 1963) and 2 for men.

Contingency tests have been used in the usual way to compare the incidence between different exposures where appropriate. When each group of animals numbered less than 40 it was possible to look up the exact significance level in binomial tables. In other cases the significance level has been approximated by the χ² test with Yates’s correction. This test is known to be a poor approximation when low frequencies are encountered (Grizzle 1967). In such cases Fisher’s exact test has been applied. Probabilities quoted in the text are for two-tailed tests and the level of statistical significance corresponds to \( P \leq 0.05 \). Where the method used yielded a single-tailed probability, the two-tailed probability has been given as double this. This is a sufficiently good approximation for the large sample sizes encountered in the present work.

Results

(i) Experiments with double hyperbaric exposures

Our first experiments required that the conditioning exposure should be to saturation so that any increase in liability to decompression revealed by the test dive could not be attributed to further gas uptake during the latter. Lever (1969) has shown that a 40 min exposure to hyperbaric nitrogen is more than sufficient to ensure complete saturation in the mouse as judged by its sensitivity to decompression. In confirmation of this we found, for first or conditioning exposures of variable duration followed after 5 min in 1 atm oxygen alone by a 5 min second (test) exposure to 10.2 atm nitrogen, that there was no significant difference in the incidence of decompression sickness after the test exposure whether the
conditioning exposure was for 20, 40 or 90 min duration (nor between 20 min and the pooled data for 40 and 90 min). In the following, the term 'saturation exposure' has therefore been applied to exposure for 40 min.

Figure 1, curve B, shows the % mortality following a single saturation exposure at various pressures and figure 1, curve A, the comparable data for conditioning saturation exposures, also at various pressures, followed after 5 min at 1 atm (in oxygen) by a test exposure to 10.2 atm nitrogen for 5 min. The mortality of the double exposure sequence is consistently higher. Thus, for the case when all exposures are to 10.2 atm nitrogen, the incidence for the single exposure is 31% and that for the double exposure 89% \((P < 0.01)\). The double exposure sequence is more lethal even though the degree of saturation in the tissues at the time of the second decompression must be lower than that at the end of the first exposure. The first exposure to pressure and decompression had therefore set up an enhanced liability to sickness, readily detectable 5 min after the decompression.

**Figure 1.** The relation between exposure pressure \(p\) (in atm \(N_2\) in the presence of 1 atm \(O_2\)) to percentage mortality for: A (■), saturation exposure to \(p\) atm \(N_2\), followed after 5 min at 1 atm by a 5 min exposure to 10.2 atm \(N_2\) (only mice dying after the second exposure were recorded); B (○), saturation exposure to \(p\) atm \(N_2\); C (▲), 5 min exposure to \(p\) atm \(N_2\). Bars indicate 95% confidence limits. The numbers against each point are the sample size.
Role of separated gas in decompression procedures

(ii) The effect of varying the time between exposures

The effect of varying the time between two exposures was next investigated, for which shorter exposure times were convenient. The relation between exposure pressure and mortality for a single 5 min exposure was first determined (figure 1, curve C), and this result allowed a suitable choice of pressures for briefer exposures. Two series of double 5 min dives were carried out: the first series at a pressure (12.2 atm N₂ + 1 atm O₂) capable by itself of producing (for a 5 min exposure) a low incidence of sickness (8%), and the second series at a pressure just below the threshold for any lethality (10.2 atm N₂ + 1 atm O₂; 0% incidence). The results are displayed in figure 2A and B, together with comparable data for a similar experiment with helium using two 2 min exposures to 12.2 atm helium (figure 2C).

![Figure 2](http://rspb.royalsocietypublishing.org/)
In all experiments there is a characteristic sharp increase in mortality as the time spent between exposures increases from zero (i.e. a single 10 min exposure), although the quantity of dissolved gas in the animals' tissues must be decreasing during the inter-dive period. This increase is followed by a slow decline towards the mortality incidence appropriate to the test exposure by itself. The minimum at 5 min interval in figure 2B is not statistically significant. It was found, in addition, that the time to the first convulsion was much shorter after the test exposure, and this is discussed later.

The effect of a succession of short multiple exposures was next tested. To allow nearly complete inert gas elimination between the exposures, a 10 min gap was chosen; exposure pressures of 10.2 atm N$_2$ in one series and 12.2 atm N$_2$ in the other were performed. The results are given in table 1. As with 5 min intervals, the incidence after the second decompression was always significantly higher than that after the first decompression. For the 10.2 atm exposure, it was also significantly higher than the incidence (0%) for a 10 min dive. Further, this elevated incidence was maintained on subsequent decompressions, even though one might expect animals that survived the first two exposures to be those more resistant to decompression sickness.

### Table 1. Multiple exposures

<table>
<thead>
<tr>
<th>Exposure pressure</th>
<th>Incidence at nth decompression</th>
</tr>
</thead>
<tbody>
<tr>
<td>atm N$_2$</td>
<td>1</td>
</tr>
<tr>
<td>10.2</td>
<td>0/56</td>
</tr>
<tr>
<td>%</td>
<td>0</td>
</tr>
<tr>
<td>12.2</td>
<td>8/75</td>
</tr>
<tr>
<td>%</td>
<td>11</td>
</tr>
<tr>
<td>10.2 + 12.2 (pooled data)</td>
<td>8/131</td>
</tr>
<tr>
<td>%</td>
<td>6</td>
</tr>
</tbody>
</table>

Since 10.2 atm N$_2$ is below the threshold pressure for sickness for single 5 min exposures, although a total incidence of 37% sickness follows four repeated exposures to this pressure, an attempt was made to estimate the threshold pressure for this multiple exposure procedure. Repeated 5 min exposures with 10 min intervals between them were carried out as before at 6.8, 8.2 and 8.8 atm N$_2$. The incidences after at least four successive exposures were 0/22, 0/37 and 1/6 respectively. In a more stringent test of the threshold, a number of 6.8 and
8.2 atm N₂ excursions were followed 10 min later by a test dive at 10.2 atm N₂ for 5 min, giving incidences of 0/16 and 1/31 respectively. It was noted that in the latter case several other animals exhibited mild symptoms of decompression sickness. It appears therefore that 8.2 atm N₂ is close to the threshold for zero incidence after multiple dives of this type. This is some 2 atm N₂ lower than the comparable threshold for single 5 min exposures, and at or slightly above the threshold for single saturation exposures.

It is probable that this threshold would be lower still for shorter intervals between the dives. One practical implication is that the old assumption in diving practice, that with repeated dives repeated within a limited period decompression was safe if done for the aggregate time under pressure, may not be safe.

(iii) The effect of varying the length of the test exposure

Increasing the length of the test dive should cause a transition from exacerbation to therapy. Such a transition is demonstrated in the results of tables 2 and 3 discussed below.

**Table 2**

First exposure of 5 min at 10.2 atm N₂ + 1 atm O₂, followed after 5 min in 1 atm O₂ by a second exposure at the former pressure.

<table>
<thead>
<tr>
<th>t/min</th>
<th>mortality after 2nd exposure</th>
<th>distribution of time of death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>incidence</td>
<td>percentage</td>
</tr>
<tr>
<td>1</td>
<td>10/25</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>7/20</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>5/55</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>8/25</td>
<td>32</td>
</tr>
<tr>
<td>40</td>
<td>7/25</td>
<td>28</td>
</tr>
</tbody>
</table>

Table 2 shows the results of a test exposure of duration ranging from 1 to 40 min applied 5 min after a 5 min conditioning exposure. The first exposure (10.2 atm N₂) had been found (figure 1, curve C) to produce no fatalities, but the lethality of all the test exposures is significantly higher. For a 5 min test exposure, mortality is significantly lower than for one of 3 or 10 min \( P = 0.024 \). The incidences of all the second exposures are significantly higher than those of a single exposure of the same duration, except after a 40 min exposure, when no difference is found. Thus a 40 min second exposure is therapeutic and the highest exacerbation occurred after a second exposure of only 1 min.
The results in table 3 show some exacerbation after test dives as short as 16 s. In these cases the conditioning exposure produces an incidence of 16 to 30% ($P > 0.1$), and if the test exposure is a ‘bounce dive’ of 16 s (6 s compression and 10 s decompression), 24% of the survivors of the first exposure die. This is a high incidence, considering that the first exposure might be expected to eliminate the susceptibles and that the degree of desaturation achieved during the 5 min between exposures would hardly be so affected by such a brief second exposure as to increase mortality so sharply. It could be suggested that these were in fact delayed deaths from the first conditioning saturation exposure. But this is impossible since all but one died within 30 to 70 s of the second decompression, and the cause of death cannot be ascribed simply to the first exposure. This is corroborated by the next set of data where a similar test excursion, but with 9 s spent at pressure, killed 67% of the survivors of the first exposure within 70 s. The difference in mortality between these two tests is highly significant ($P = 0.01$) even though the durations of the test exposures differ by only 9 s. Mortality was even higher when the test exposure was prolonged to 5 min, but not significantly so ($P > 0.05$). An additional prolongation of the test exposure to 40 min led to a significant decline in mortality from the 5 min level ($P < 0.01$). Of the 20 deaths after a second 40 min exposure, 13 occurred within 5 min. If this figure is compared with the pooled data for death after the first exposure, it is found not to be significantly different ($P > 0.1$), so that, as in the results of table 2, we find that a second exposure of 40 min removes all ‘memory’ of the prior exposure so far as the incidence level can detect. However, an interesting difference does appear between the two types of run (tables 2 and 3). The exacerbating effect of a 5 min
Conditioning exposure on the mortality of the test dive is greatly reduced if the latter itself lasts as long as 5 min. But with a saturation conditioning exposure, this dip in the mortality time of test exposure curve was not seen.

(iv) Times of death

The time at which the first signs of sickness occur after decompression is a rather neglected parameter, which can provide some information on the rate of development of the sickness. Thus Lever (1969, 1971) found that the distribution of the time to first convolution for mice exposed to single excursions with 10 to 15 atm nitrogen ranged from 30 s to more than 10 min, half the animals dying in about 3½ min (table 4), and for single 5 min exposures our data show the same wide distribution of onset times. But in contrast multiple 5 min exposures show a sharp deviation from this pattern with most animals dying within 90 s, and over half the animals dying within 45 s. The pattern after 2 min helium exposures is similar, though events seem to occur a little more rapidly, just as they do after single exposures to this gas for which the mean onset time is about 1 min. With double exposures to nitrogen, in which the second exposure lasts 10 min or more, the distribution of onset times occupies an intermediate position, differing significantly both from that for 5 min multiple exposures and from that for a single 5 min exposure. Thus the deaths between 30 and 75 s were 4% for single 5 min exposures, 52% for multiple 5 min exposures, and 33% for double exposures with test exposures $\geq$ 10 min. We also found that for double exposures with 40 min (saturation) second exposures, some 'memory' of the conditioning exposure remained, showing itself not in the overall lethality, but in a shift to earlier time of death.

**Table 4**

<table>
<thead>
<tr>
<th>Time elapsed after decompression (s)</th>
<th>Single saturation exposures (Lever 1969)</th>
<th>Double exposures to various pressures</th>
<th>Multiple double exposures to saturation pressures</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 s</td>
<td>—</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30 s</td>
<td>2</td>
<td>7</td>
<td>36</td>
</tr>
<tr>
<td>45 s</td>
<td>7</td>
<td>25</td>
<td>73</td>
</tr>
<tr>
<td>60 s</td>
<td>10</td>
<td>38</td>
<td>92</td>
</tr>
<tr>
<td>75 s</td>
<td>11</td>
<td>43</td>
<td>96</td>
</tr>
<tr>
<td>90 s</td>
<td>23</td>
<td>43</td>
<td>94</td>
</tr>
<tr>
<td>2 min</td>
<td>34</td>
<td>50</td>
<td>94</td>
</tr>
<tr>
<td>5 min</td>
<td>64</td>
<td>80</td>
<td>94</td>
</tr>
<tr>
<td>10 min</td>
<td>98</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Cumulative incidence of first convolution after various exposures (%)
(i) **Physical behaviour of the gas phase**

Our results and their deviation from the behaviour predicted by Haldane-derived models may most simply be explained by supposing that gas separation occurs in the body after decompression, without causing symptoms. Indeed considerable insight into the physical principles involved may be gained by viewing our results in terms of a single extra-vascular bubble. Whilst this model is obviously a gross oversimplification, it does supply a sound physical basis from which the much more complex real-life situation may be explored.

![Figure 3. Schematic representation of processes occurring during a double exposure.](image)

- (a) Pressure profile of exposure.
- (b) Partial pressure of inert gas dissolved in the tissue.
- (c) Moles of gas in the bubble.
- (d) Threshold for symptoms produced by bubbles.
- (e) Pressure level (~ 0.9 atm, see text) at which inert gas partial pressure equals that in the bubble.

After a first decompression we assume that a bubble is rapidly nucleated. The bubble will be in pressure equilibrium with its surroundings so that, allowing for oxygen, carbon dioxide and water vapour partial pressures, and for surface tension, the partial pressure of nitrogen in it will be somewhat less than 1 atm (say 0.9 atm \( \text{N}_2 \)). The partial pressure of nitrogen in solution in the tissues will initially be high, and will fall more or less exponentially towards zero, since the animal is breathing pure oxygen. While the tissue partial pressure is greater than that in the bubble, the latter will grow (figure 3). The tissues will eliminate nitrogen both by the usual perfusion-limited pathway into venous blood and also by diffusion into the bubble. On both counts we may predict that the tissue gas partial pressure will fall at first rather rapidly, and then more slowly as the gradient in gas partial pressures declines. Once the tissue (dissolved) gas partial pressure falls below that in the bubble, the decay of the latter contributes dissolved gas back into the tissue, further slowing the fall in tissue nitrogen partial pressure. We thus predict initially a short period of relatively rapid bubble growth, giving way gradually to a more protracted period of bubble decay. The kinetics of bubble growth under such conditions has been investigated by Nims (1951) in a semi-quantitative manner. He examined equations of the general form

\[
d(Ns/N)/dt = a_1 \exp(-k_1 t) - a_2 \exp(-k_2 t),
\]
where \( N_s \) is the number out of \( N \) subjects exhibiting symptoms at time \( t \), and the constants \( a_1 \) and \( a_2 \) are related to the symptom intensity (and hence to bubble size or pressure) and \( k_1 \) and \( k_2 \) are related to the time constants for growth and decay. Such equations successfully described the rate of onset of decompression sickness in men under hypobaric pressures.

On the basis of this simple model, the subliminal liability to decompression sickness produced by the conditioning dive (and revealed by the test dive) would be expected to increase rapidly after the conditioning dive and then decay away more slowly. This is exactly the pattern apparent in figure 2. The quantitative differences between the three situations in the figure also parallel the expected changes for bubble growth and decay. For example, figure 2C gives the results

<table>
<thead>
<tr>
<th>Table 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>( x_2 = \text{mole fraction solubility} )</td>
</tr>
<tr>
<td>( \text{water 25 °C} )</td>
</tr>
<tr>
<td>( 10^5 x_2 )</td>
</tr>
<tr>
<td>helium</td>
</tr>
<tr>
<td>nitrogen</td>
</tr>
</tbody>
</table>


for double dives with helium, and these provide a useful check of this interpretation. Calculations on a perfusion-limited model show that the fatty tissues in man have a half-life some 2.5 times faster for helium than nitrogen (Miller 1966), and recent experimental studies have shown this to be true for mice also (Lever 1969). For a given partial pressure difference, it has been shown (Epstein & Plesset 1950) that bubble growth rate is proportional to \( D x_2 \), where \( D \) is the diffusion coefficient and \( x_2 \) the solubility for the given gas-liquid system. Thus helium bubbles will grow somewhat faster than nitrogen bubbles (table 5), and we would predict both that the bubble growth and the bubble decay phases will be shorter than for nitrogen and that the initial rate of increase of the size of helium bubbles will be faster than that for nitrogen. Figure 2C (compared with figure 2A) shows all these features: the rapid increase to a large maximum, followed by rapid decay to control levels. The time to death is also consistently shorter than with nitrogen (table 4).

According to this simple picture, the test dive behaves as a bubble amplifier. During the dive itself the bubble decays somewhat, but the tissues around it begin to saturate with gas once more, so that after the second decompression the period of rapid bubble growth acts on the preformed bubble, and it achieves more quickly the size required to cause symptoms. This is reflected in the much earlier times of death for second or subsequent 5 min dives recorded in table 4. As the second or test exposure proceeds; the amount of gas in the bubble decreases by diffusion,
whilst the amount of dissolved gas in the surrounding tissues increases by uptake from perfusing blood. The amplification of the bubble by the second decompression thus depends both on the accumulated tissue nitrogen, which will increase with the length of the second excursion until saturation is achieved, and on the bubble size, which decreases with time spent at pressure. The ability of such a bubble to grow to a certain critical size after decompression thus depends on the balance of these two effects. The whole process may be summarized pictorially as in figure 3.

(ii) Limitations of the extravascular bubble model

We find that certain deviations from this simple extravascular bubble model may be assigned to causes of a more physiological nature. The limitations of this model revealed by our data are summarized below, and a simple physiological explanation is offered later.

First, table 3 shows the effect of varying the length of the test exposure over a wide range after a moderately severe saturation exposure. A test exposure as short as 16 s produced as many deaths as the conditioning exposure of 40 min, and a test exposure only 9 s longer produced a significantly higher incidence. Such effects occur too rapidly to be accounted for on the basis of bubble dynamics and gas uptake, and their origin must be sought in the more rapidly developed effects in the vascular system.

Secondly, the rates of decay exhibited in figure 2 are too high to be accounted for on the basis of the physical decay of bubbles in the tissues. This conclusion follows from the calculations based on the equations of Epstein & Plesset (1950) and on the more recent studies of Van Liew & Hlastala (1969). This suggests that in addition to the diffusion pathway another mechanism exists by which bubbles may be eliminated.

Furthermore, there are two other possible discrepancies. One is that the simple model would predict an increasing incidence after successive dives in a series of dives, yet the data in table 1 fail to reveal any significant trends in mortality after the second exposure. Although the latter situation may arise through selective survival of progressively more resistant mice, it seems possible that a further explanation is required.

The other possible discrepancy arises from the results in table 2, which show the effect of increasing the length of the test exposure after a 5 min conditioning exposure. Over 1 to 5 min the incidence of death declines, indicating that bubble decay is predominating. At 10 min, however, the incidence has risen again. The increase in time to death, however, indicates that we may attribute this partly to the increase of tissue nitrogen alone initiating new sites of bubble growth, but this is not entirely satisfactory, for the incidence is significantly higher than that for a single 10 min exposure, even if only late (> 75 s) deaths are counted.
Role of separated gas in decompression procedures

(iii) Physiological interpretation

The failures of the extravascular bubble model can be accounted for by considering the behaviour of bubbles in the vascular system. There is now a considerable body of evidence, both direct and indirect, to support the following picture (see, for example, Elliott 1969; Gramenitskii & Savich 1965; Spencer & Campbell 1968). After decompression, bubbles are formed in a few peripheral areas, some of which eventually appear passing centrally along the vena cava. The first intravascular bubbles appear always to be intravenous, but subsequently they are observed in the aorta and peripheral arteries of severely affected animals, often coincidentally with the first convulsion.

We assume that the lungs filter separated gas from the venous blood, and that unless they become overloaded with gas, none is allowed into the left side of the heart. If we also assume that separated gas at the lung can be eliminated into the alveoli, but at a limited rate, and that the incidence of lethal decompression sickness is related to the amount of gas at the heart and lungs rather than in the periphery, then the incidence and time course of decompression sickness will be related to the rate of arrival of separated gas at the lung. This in turn will depend chiefly on the rate of nucleation of bubbles, their rate of growth in situ, and the rate of access of separated gas to the vascular system. It could also depend on the rate of transport of such bubbles through the venous system to the lung, but normally this should be rapid unless circulatory failure occurs.

Our work yields no direct evidence on nucleation, but reference to figure 2 suggests that bubbles had formed and grown sufficiently to elevate the risk from a second dive within 1 min of the first decompression. Thus nucleation appears to occur rapidly, at least in the animals that are destined to die after the second dive.

If this is the case, then the rate-controlling process is almost certainly the bleeding off of bubbles into the vascular system from growing gas pockets. This is consistent with the degree of success of the simple picture of the incidence of decompression sickness being related to the growth and decay of an extravascular bubble as outlined above; and the failures of the simple picture may now largely be accounted for on the basis of bubble redistribution. We may postulate that on compression, many bubbles trapped in the periphery are reduced in size, released, and move centrally. If this process contributes enough gas to the critical central area and is followed soon after by decompression, symptoms will be observed very rapidly. The effect of a ‘bounce dive’ is thus to accelerate the transfer of separated gas from growing peripheral gas pockets to the centre, perhaps with a shower of small intravenous bubbles. The release of such bubbles depends primarily on their decrease in size upon application of pressure, although the restoration of locally occluded blood flow could well also contribute. If the pressure is quickly reduced again before the new bubbles at the lung have been eliminated, acute decompression sickness should be produced very rapidly. This is precisely what is observed following the very short test dives of table 3.
explanation is correct, the same table shows that the process of redistribution in mice is significantly advanced after a second compression of only 16 s.

On this basis the anomalously high decay rates observed in figure 2 are seen to arise from the bleeding off of separated gas from the tissues into the vascular system as well as by diffusion-controlled resorption in situ. This redistribution would be most marked at the beginning of a test dive, and could mask the diffusive decay occurring throughout the test dive. It should thus have a levelling effect on the size of the remaining tissue bubbles, which might account for the apparent constant incidence between the second and subsequent decompressions.

(iv) Current decompression practice

It is instructive to consider our results in the context of three current methods for formulating decompression tables.

The first two methods are based on the ideas of Haldane. In the first (see, for instance, Workman 1969), the quantity of dissolved gas accumulated in many tissues of the body during one or more dives is calculated. It is supposed that on decompression there is a maximum degree of supersaturation that can be tolerated, and must not be exceeded, in any tissue if sickness is to be avoided. The tolerable supersaturation, or decompression ratio, is determined by trial and error as the maximum ratio between total external pressure and tissue gas partial pressure that just prevents symptoms from appearing. It is assumed that with this ratio no phase changes occur, and gas uptake and elimination are not affected.

The second method (Hempleman 1960, 1969) differs in considering the quantity of gas in one critical tissue only, and in assuming that on decompression to the maximum symptomless supersaturation, 'silent' bubbles are formed, which cause gas elimination to be slower than uptake. In keeping with the Haldane postulate, the behaviour of the silent bubbles is neglected except in so far as they restrict gas transport.

In both these methods, on which current tables are based, the maximum tolerable pressure drop is applied at the beginning of the decompression in order to provide a high driving force for gas elimination. The third method (Hills 1970), however, departs radically from the Haldane postulate. It assumes that bubble formation occurs instantaneously with any degree of supersaturation, and advocates a slow initial phase of decompression, calculated on the basis of avoiding any supersaturation.

Our results are incompatible with the Haldane-type models, which cannot generate an increasing susceptibility to decompression sickness as time elapses after decompression. Equally, the subsequent decline in susceptibility takes place too fast to be accounted for by gas elimination alone in the presence of a separated gas phase. But one objection to this conclusion must be considered here. To obtain an unambiguous and objective measure of decompression sickness, and a statistically useful incidence rate, it is necessary, with mice, to use rather severe decompression routines. The sickness produced in the mice is probably best compared
with ‘chokes’ in man. The latter almost certainly involve bubbles in the pulmonary vessels; and it has been found (Lever et al. 1966) that in mice there was, with exposures such as now used, a considerable accumulation of gas in the right heart. It could be suggested, therefore, that our work refers only to conditions where the safe supersaturation ratio has been grossly exceeded and is not applicable to the Haldane-type procedure, which is designed to reduce even minor sickness to a minimum. But it should be noted that in several cases our first conditioning dives produced no deaths (e.g. figure 2B and table 2), and these routines showed no major differences from those in which the first dive produced fatalities. Similarly, we found that multiple exposures of 5 min each at a pressure 2 atm below the safe limit for a single 5 min dive caused deaths. Further, it is well established that current Haldane-type decompression procedures do not abolish decompression sickness, but reduce it below an incidence, usually regarded as acceptable, of 2 %, within which occasional very severe cases occur (Golding et al. 1960). Finally, it may be noted that the experiments by Hempleman, using ‘joint’ bends in goats, which led to his revision of decompression procedures, produced anomalous results fully consistent with those presented here. We believe, therefore, that there is no good reason for doubting that the processes unmasked in our experiments are applicable to less severe decompression procedures and to larger animals.

One further qualification is necessary. We have suggested that the decline of susceptibility in our experiments after initial rise is greatly accelerated by transfer of gas from the periphery to the centre to be eliminated at the lungs. This is a feature that may be peculiar to our particular procedures, and with less severe procedures one could be dealing purely with the local effects of separated gas. Under these conditions, one would still see the rise in susceptibility after decompression, but the subsequent decline should be much slower. It would be instructive to repeat experiments of the type in figure 2, with milder procedures in large animals.

Our results cannot be reconciled even with Hempleman-type models. Though these postulate separated gas, it is supposed only to interfere with gas elimination. Such interference is, in fact, very likely to occur, for two reasons; the first is simple occlusion of blood vessels in the neighbourhood; the second is that the formation of a bubble abstracts gas from a considerable area of tissue around it, for example a nitrogen-containing bubble could clear about 70 times its own volume in aqueous solution or 15 times in a non-aqueous solution. But even if our results were incorporated into the Hempleman model, by means of the suggestion that the interference with rate of gas elimination increased for a period after decompression (as the bubbles grew and desaturated their surroundings), an increasing liability to decompression sickness for the period immediately after decompression cannot be accounted for.

Our results do not provide a test for the Hills type of procedure, since the latter rests on an attempt to prevent phase separation, but they provide at least a partial vindication of the approach. They are, in fact, incompatible with the
extreme form of Hills's theory, in which it is supposed that if gas separation occurs after decompression, complete phase equilibrium occurs immediately; for, in that case, bubble growth over a 5 min period could not occur. But if phase equilibrium requires an appreciable time, then a situation much as we have postulated arises, with separated gas and supersaturated tissues both present. Our results do not however necessarily imply that separated gas is present with any decompression. It may be that there is a significant degree of supersaturation at which nucleation is vanishingly infrequent, above which is an intermediate zone where gas separation is symptomless at least for single dives. Thus in figure 1, curves A and B, where the incidence for a single saturation dive is compared with that for the same exposure followed by a second short dive, the threshold (0% incidence) of 7.7 atm N\textsubscript{2} for the single dive is lowered to 4.4 atm N\textsubscript{2} for the double dive. A supersaturation of 4.4 atm N\textsubscript{2} might therefore represent the level below which nucleation in the mouse does not occur. On the other hand, one cannot exclude the possibility that a more sensitive test would lower the supersaturation limit still further.

The question arises, if the physical basis of the conventional tables is incorrect, as to why they are relatively successful in practice. In fact, the principles involved have been applied very empirically, the estimates of tolerable supersaturation and gas elimination rates being adjusted as experience required. It may be that the effects we have described run as rapid a time course in man as in the mouse; in that case, empirical adjustments to notional gas elimination rates would be possible, assuming decompression stages did not occur at intervals less than 5 min. Indeed, there is reason to believe that the empirically developed tables have taken practical account of the consequences of gas separation, in view of the successful use over many years of 'surface decompression' and 'decanting'. (This technique was used by the late Captain G. C. C. Damant before the last war, and during the war further developed by H.M.S. *Tedworth* and investigated by K. W. Donald and W. M. Davidson at the Admiralty Experimental Diving Unit; modern accounts are available for diving (Workman 1969) and caisson work (Walder 1969).) In these procedures a diver or caisson worker is rapidly decompressed from an unsafe depth to atmospheric pressure, and then rapidly transferred to a decompression chamber; here he is recompressed and then undergoes a normal decompression. With this procedure, the safe decompression ratio is exceeded by a large margin, even if for a time not longer (according to British regulations) than 5 min. The success of this procedure strongly suggests that normal decompression procedures have been adjusted to deal with a situation in which a separated gas phase is present. Similarly, in therapeutic recompression, Goodman & Workman (1965) have stressed the danger of repeated tissue nitrogen saturation when there is clinical evidence of bubble-formation, and have developed a successful 'minimal recompression' procedure using oxygen. One may note, too, that historically the success of the tables current at any particular time has not allowed successful extrapolation, using the same principles, to greater depths; and their evolution shows a
continuous series of adjustments as greater pressures or longer exposures have been attempted. It could well be that this has happened as a consequence of forcing the empirical data into a physically inadequate Procrustean bed. The main conclusions from our experiments, that after decompression there can be growth, decay and transport within the body of a separated gas phase, do not make the formulation of an adequate theory any easier. But at least it appears probable that no one existing theory is entirely correct, and our present experiments show that decompression procedures need formally to take account of separated extravascular gas, of supersaturated tissues in its vicinity, and of the behaviour of intravascular bubbles.

This work was supported in part by the U.S. Office of Naval Research (Physiological Branch).

References


